VOLUME 67 *February, 1953* NUMBER 2

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS

Epidemiology of Tuberculosis. GAYLORD W. ANDERSON 123

Tuberculosis in the Island of Puerto Rico. J. RODRÍGUEZ PASTOR AND JOSÉ L. JANER 132

Cardiopulmonary Function in the Pulmonary Form of Boeck's Sarcoid and Its Modification by Cortisone Therapy. JOHN H. MCCLEMENT, ATTILIO D. RENZETTI, AARON HIMMELSTEIN, AND ANDRE COURNAND 154

The Effect of Streptomycin Therapy on the Bronchocavitary Junction and Its Relation to Cavity Healing. OSCAR AUERBACH, HARRY L. KATZ, AND MAURICE J. SMALL 173

The Effect of Corticotropin (ACTH), Dihydrostreptomycin, and Corticotropin-Dihydrostreptomycin on Experimental Bovine Tuberculosis in the Rabbit. JAMES M. BACOS AND DAVID T. SMITH 201

Withdrawal Symptoms upon Discontinuance of Iproniazid and Isoniazid Therapy. IRVING J. SELIKOFF, EDWARD H. ROBITZEK, AND GEORGE G. ORNSTEIN 212

Lethal and Cytologic Effects of Lysozyme on Tubercle Bacilli. QUENTIN N. MYRVIK, RUSSELL S. WEISER, AND HILDA D. AGAR 217

Collapse Therapy for Tuberculous Psychotic Patients. GEORGE N. J. SOMMER, JR., ABRAHAM M. BALTER, HAROLD S. HATCH, AND HAROLD J. MUENDEL 232

Case Report:

Hepatic Tuberculosis in a Patient with Sickle-Cell Anemia Who Died of Fatal Post-Transfusion Hepatitis. EDWARD R. CHRISTIAN 247

Notes:

Prothrombin Time During Para-Aminosalicylic Acid Therapy. Two Thousand Determinations in 400 Patients. LEMBIT NORVIIT AND BO CARSTENSEN 258

Sensitivity of *Actinomycetales* to Isonicotinic Acid Hydrazide, Compared to Other Synthetic and Antibiotic Antituberculosis Agents. SELMAN A. WAKSMAN AND HUBERT A. LECHEVALIER 261

The Nature of the Virulence of Human and Bovine Types of Tubercle Bacilli for the Rabbit. MAX B. LURIE 265

Correspondence: Lung Immobilizer Therapy in Pulmonary Tuberculosis. JOHN D. STEELE AND GEORGE C. OWEN 267

American Trudeau Society:

Resection of Residual Necrotic Lesions. A Report of the Committee on Therapy 268

The Current Status of Isoniazid in the Treatment of Tuberculosis. A Report of the Committee on Therapy 269

Notes 270

Books 272

Abstracts 29

ANNUAL MEETING—LOS ANGELES, CALIF.
May 18–22, 1953

See inside back cover

Published Monthly at Mount Royal and Guilford Avenues, Baltimore 2, Maryland by the National Tuberculosis Association • Business Off., 1790 Broadway, New York 10, N. Y.

Copyright 1953, by the National Tuberculosis Association

PRINTED IN U. S. A.

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
Medical Section of National Tuberculosis Association

EDITOR
WALSH McDERMOTT
New York, N. Y.

CONSULTING EDITOR
ESMOND R. LONG
Philadelphia, Pa.

EDITOR OF ABSTRACTS
LAWRENCE B. HOBSON
New York, N. Y.

Helen W. Miller, *Editorial Secretary*

EDITORIAL BOARD

John D. Adcock, M.D., Ann Arbor, Mich.
William H. Feldman, D.V.M., Rochester, Minn.
Byron F. Francis, M.D., Seattle, Wash.
Max B. Lurie, M.D., Philadelphia, Pa.
Donald L. Paulson, M.D., Dallas, Tex.
Philip E. Sartwell, M.D., Baltimore, Md.
John D. Steele, M.D., Milwaukee, Wis.
William B. Tucker, M.D., Minneapolis, Minn.
Arthur J. Vorwald, M.D., Saranac Lake, N. Y.

BUSINESS MANAGER
HENRY W. STEVENS

NOTICE TO SUBSCRIBERS AND CONTRIBUTORS

THE AMERICAN REVIEW OF TUBERCULOSIS is published by the National Tuberculosis Association and issued monthly about the first of the month. THE AMERICAN REVIEW OF TUBERCULOSIS is the official journal of the American Trudeau Society. A volume includes six numbers and begins with the January and July numbers.

Subscription: The subscription price of the REVIEW is $12 for the calendar year. Checks should be made payable to Collier Platt, Treasurer. The price of single copies is $1.50 postpaid.

Character of the Review: The REVIEW invites the submission of original manuscripts on any phase of tuberculosis, nontuberculous pulmonary diseases, and related subjects of interest.

MANUSCRIPTS

Contributors are requested to pay particular attention to the following rules governing the preparation of manuscripts. Failure to follow these rules is a frequent cause of delay in the publication of articles.

Manuscripts should be sent in duplicate to the office of the Editor, Dr. Walsh McDermott, 1790 Broadway, New York 19, N. Y., mailed flat, and transmitted by first-class mail with postage for return if not acceptable. They should be in English, double-spaced, typewritten on one side of the page with wide margins. Tabular data should not be included in the text but should be presented in separate tables with appropriate reference in the text. All cases of pulmonary tuberculosis should be classified according to the 1950 edition of *Diagnostic Standards and Classification of Tuberculosis* published by the National Tuberculosis Association. All case reports should be written in complete sentences. Authors should exercise particular care in the preparation, notation, and description of figures and tables. The form of reference used in the REVIEW should be carefully followed and references should be checked for accuracy. Each table must be accompanied by a descriptive title and a suitable legend must be provided for each figure. Drawings must be made with india ink and all lettering should be made with a stencil. The quality of the reproduction of a roentgenogram depends upon both the quality of the original picture and of the glossy print obtained from photographing that picture. If a contributor does not have facilities available, preparation of figures or reproduction of roentgenograms may be handled through the REVIEW office. In those circumstances, the contributor should supply a neat, properly proportioned, and suitably entitled drawing or the original roentgenogram, and will be expected to defray the cost of these services.

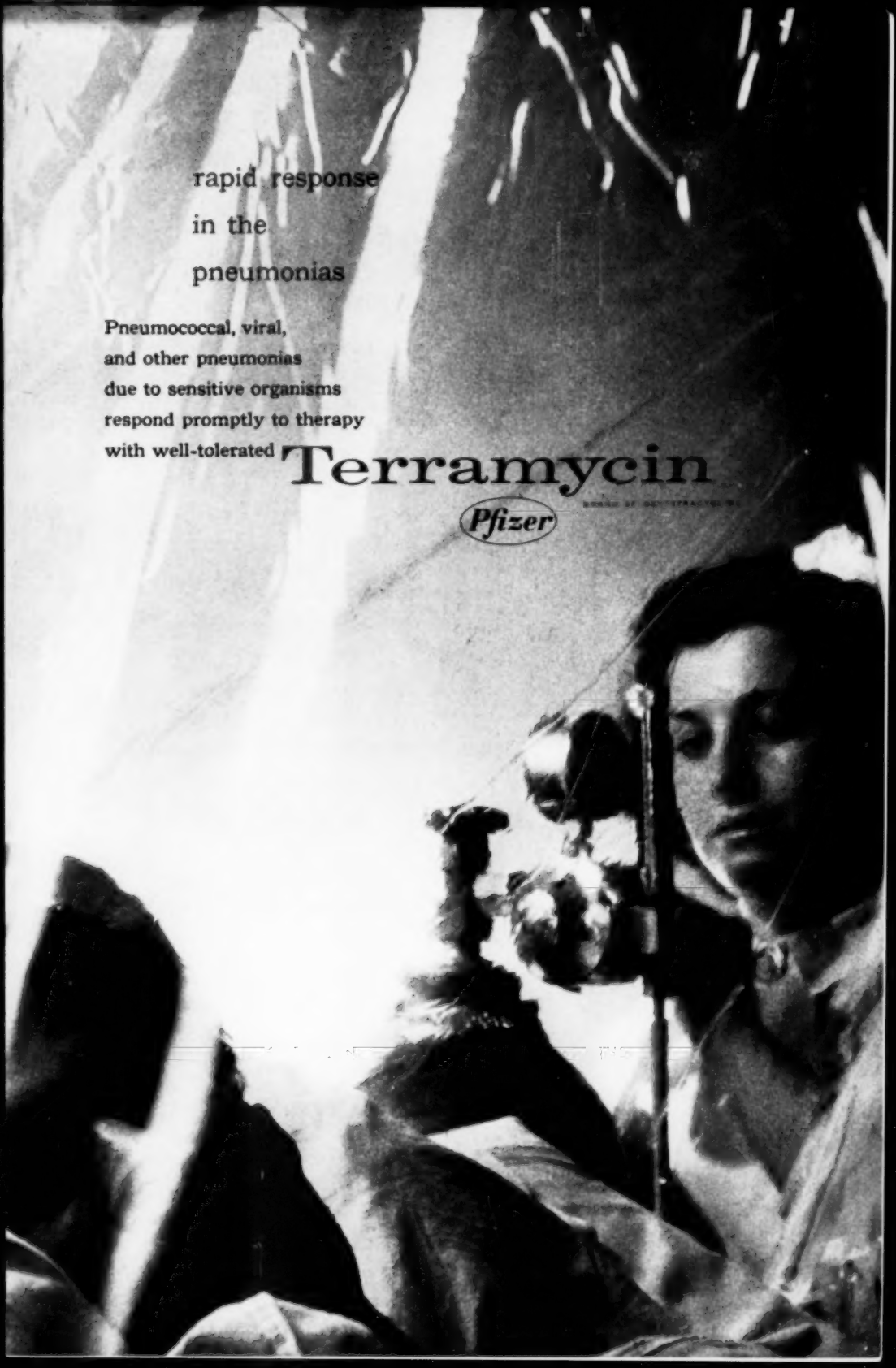
The publishers will not be responsible for manuscripts, illustrations, etc., lost in transit. In order to save expense for authors' corrections in proof, manuscripts should be carefully revised by the author before submission.

Reprints: Fifty reprints without covers of articles will be furnished to authors free of charge when requested in advance. Additional reprints may be ordered.

Advertising: Rates will be furnished by THE AMERICAN REVIEW OF TUBERCULOSIS, 1790 Broadway, New York 19, N. Y. on request.

The Publishers reserve the right to decline any advertising submitted and to censor all copy. Acceptance of an advertisement does not constitute official endorsement of the product advertised.

Entered as second-class matter March 9, 1917, at the post office at Baltimore, Md., under the Act of August 24, 1912. Acceptance for mailing at a special rate of postage provided for in section 1103, Act of October 3, 1917. Authorized on July 2, 1918.


rapid response
in the
pneumonias
Pneumococcal, viral,
and other pneumonias
due to sensitive organisms
respond promptly to therapy
with well-tolerated
Terramycin
Pfizer

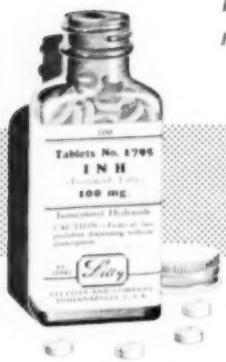
For the Treatment of Tuberculosis

The favorable results obtained with far-advanced cases have not yet established the exact position of 'INH,' but they are accepted as evidence of great promise for its wider use in the treatment of tuberculosis.

For the present, 'INH' is recommended in treating cases of active tuberculosis due to streptomycin-resistant organisms or those in which the patient has not responded to streptomycin or other treatment.

'INH' is supplied in 100-mg. tablets (scored) in bottles of 100, 1,000, and 5,000.

Eli Lilly and Company
Indianapolis 6, Indiana, U.S.A.



Lilly

TABLETS 'INH'

(ISONIAZID, LILLY)

Meat...

and the Therapeutic Value of Adequate Protein

Much evidence can be cited in favor of a high protein intake after surgery, trauma, infection, or burns. In supporting the many anabolic and defense mechanisms of the organism in physiologic stress,[1] high-quality protein—such as that of meat—assumes the status of an important therapeutic agent.[2]

Phagocytic activity,[3] formation of antibodies,[4] and rapid healing of wounds[5] are favorably affected by ample protein nutrition. Remission of peptic ulcer,[6] improved resistance to infectious disease,[4] and maintenance of plasma proteins after surgery[7] are other therapeutic effects attributed to an ample protein intake. In the management of ulcerative colitis, protein represents a primary need.[8] Recent advances in the treatment of extensive burns and of hepatic disease emphasize the value of high protein feedings.[9]

These experimental and clinical findings establish the therapeutic value of high protein intake.[10] To assure therapeutic protein adequacy, the dietary should provide a liberal margin of protein over normal requirements.

Meat is an important source of high-quality protein, containing essential as well as nonessential amino acids. In addition, it supplies significant amounts of B group vitamins and of iron, phosphorus, and other needed minerals.

REFERENCES

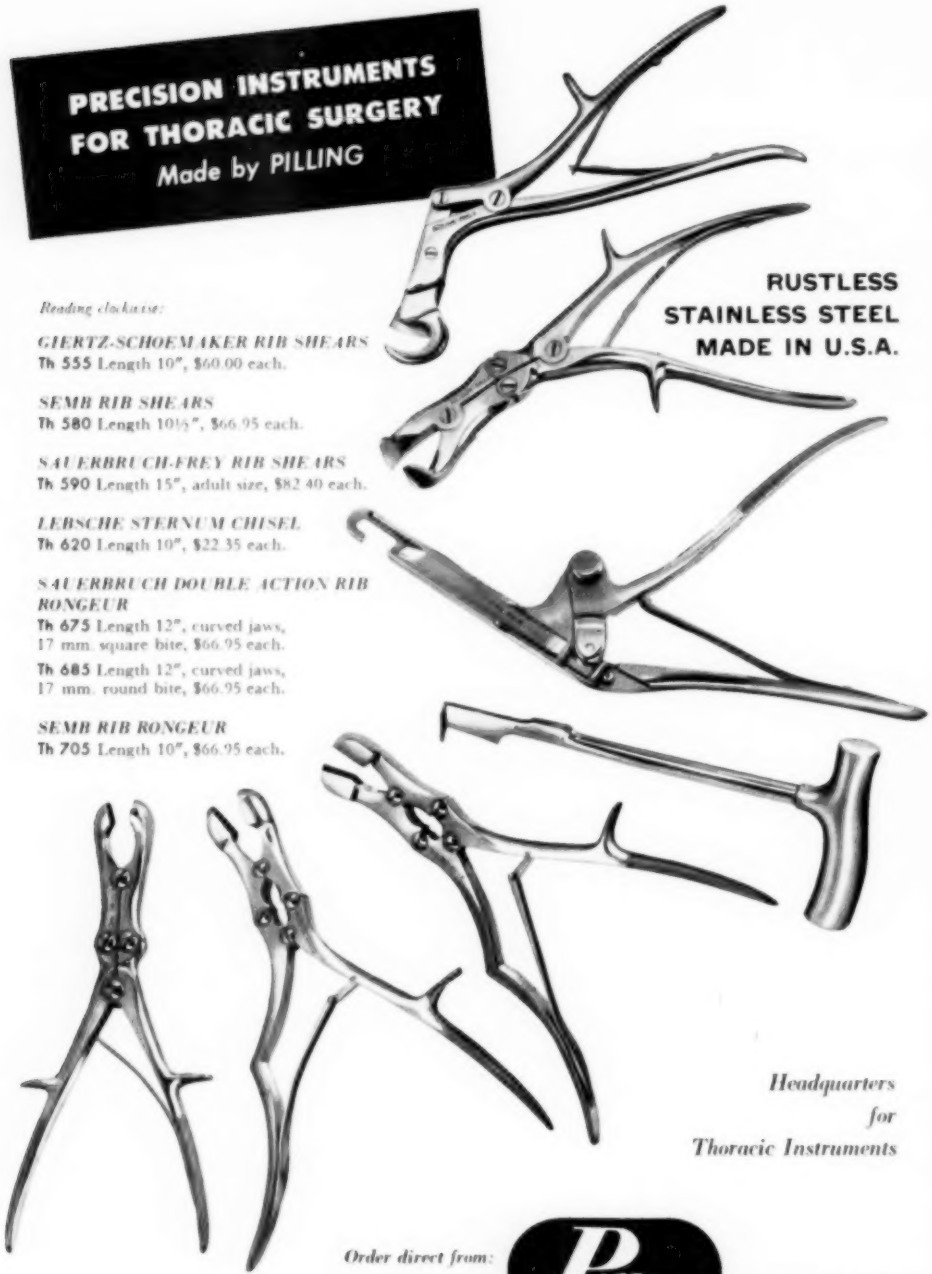
1. Rawdin, I. S., and Gimbel, N. S.: Protein Metabolism in Surgical Patients, J.A.M.A. *144*:979 (Nov. 18) 1950.
2. Mann, G. V., and Stare, F. J.: Nutritional Needs in Illness and Disease, in Handbook of Nutrition, American Medical Association, New York, The Blakiston Company, 1951, chap. 17.
3. Mills, C. A., and Cottingham, E.: Phagocytic Activity as Affected by Protein Intake in Heat and Cold, J. Immunol. *47*:505 (Dec.) 1943.
4. Cannon, P. R.: The Importance of Proteins in Resistance to Infection, J.A.M.A. *128*:960 (June 2) 1945.
5. Harvey, S. C., and Howes, E. L.: Effect of High Protein Diet on the Velocity of Growth of Fibroblasts in the Healing Wound, Ann. Surg. *97*:641 (May) 1933.
6. Co Tui, et al.: Hyperalimentation Treatment of Peptic Ulcer with Amino Acids and Dextri-Maltose, Gastroenterology *5*:5 (July) 1945.
7. Lund, C. C., and Levenson, S. M.: Protein in Surgery, J.A.M.A. *128*:95 (May 12) 1945.
8. Welsh, C. S.; Adams, M., and Wakefield, E. G.: Metabolic Studies on Chronic Ulcerative Colitis, J. Clin. Investigation *16*:161 (Jan.) 1937.
9. Cannon, P. R., et al.: Recent Advances in Nutrition with Reference to Protein Metabolism, Lawrence, Kansas, University of Kansas Press, 1950.
10. McLester, J. S., and Darby, W. J.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, 1952, p. 19.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute

Main Office, Chicago...Members Throughout the United States

PRECISION INSTRUMENTS FOR THORACIC SURGERY
Made by PILLING



RUSTLESS STAINLESS STEEL MADE IN U.S.A.

Reading clockwise:

GIERTZ-SCHOEMAKER RIB SHEARS
Th 555 Length 10", $60.00 each.

SEMB RIB SHEARS
Th 580 Length 10½", $66.95 each.

SAUERBRUCH-FREY RIB SHEARS
Th 590 Length 15", adult size, $82.40 each.

LEBSCHE STERNUM CHISEL
Th 620 Length 10", $22.35 each.

SAUERBRUCH DOUBLE ACTION RIB RONGEUR
Th 675 Length 12", curved jaws, 17 mm. square bite, $66.95 each.
Th 685 Length 12", curved jaws, 17 mm. round bite, $66.95 each.

SEMB RIB RONGEUR
Th 705 Length 10", $66.95 each.

Headquarters for Thoracic Instruments

Order direct from:
GEORGE P. Pilling & SON CO.
3451 WALNUT STREET • PHILADELPHIA

a broad spectrum dietary supplement

When anorexia interferes with the intake of needed foods in adequate amounts, the resultant effect on the nutritional status of the tuberculous patient is considerably more apt to involve deficiency in several nutrients than in one particular nutrient. As a consequence, unpredictable subclinical deficiency states may arise which predispose to a questionable prognosis. The rationale of prophylactic therapy against nutritional deficiencies, therefore, calls for a dietary supplement of broad nutrient spectrum capable of improving the intake of many nutrients.

The dietary supplement Ovaltine in milk enjoys long-established usage in clinical practice. As shown by the appended table, it supplies notable amounts of virtually all nutrients known to take part in metabolism. Its biologically complete protein provides an abundance of all the essential amino acids. It is delightfully palatable, easily digested, bland, and well tolerated.

Ovaltine is available in two varieties, plain and chocolate flavored, thus allowing choice according to preference. Serving for serving, both are virtually alike in their wealth of nutrients.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three Servings of Ovaltine in Milk Recommended for Daily Use Provide the Following Amounts of Nutrients

(Each serving made of ½ oz. of Ovaltine and 8 fl. oz. of whole milk)

MINERALS		VITAMINS	
*CALCIUM	1.12 Gm.	*ASCORBIC ACID	37 mg.
CHLORINE	900 mg.	BIOTIN	0.03 mg.
COBALT	0.006 mg.	CHOLINE	200 mg.
*COPPER	0.7 mg.	FOLIC ACID	0.05 mg.
FLUORINE	3.0 mg.	*NIACIN	6.7 mg.
*IODINE	0.15 mg.	PANTOTHENIC ACID	3.0 mg.
*IRON	12 mg.	PYRIDOXINE	0.6 mg.
MAGNESIUM	170 mg.	*RIBOFLAVIN	2.0 mg.
MANGANESE	0.4 mg.	*THIAMINE	1.7 mg.
*PHOSPHORUS	980 mg.	*VITAMIN A	3,700 I.U.
POTASSIUM	1300 mg.	VITAMIN B12	0.005 mg.
SODIUM	560 mg.	*VITAMIN D	420 I.U.
ZINC	2.6 mg.		

*PROTEIN (biologically complete)	32 Gm.
*CARBOHYDRATE	65 Gm.
*LIPIDS	30 Gm.

*Nutrients for which daily dietary allowances are recommended by the National Research Council.

Announcing

a new antibacterial combination

Gantricillin is the new combination of Gantrisin 'Roche' (the single, more soluble sulfonamide) plus penicillin.

Gantricillin is recommended for infections susceptible to penicillin or sulfonamides. It is especially useful when the causative organisms are more susceptible to the combination than to either drug alone. Each scored tablet contains 0.5 Gm Gantrisin and 100,000 units of crystalline penicillin G potassium.

Hoffmann-La Roche Inc., Nutley 10, N. J.

GANTRISIN ®—brand of sulfisoxazole
GANTRICILLIN TM

THE AMERICAN REVIEW
OF
TUBERCULOSIS

VOLUME 67 *February, 1953* NUMBER 2

EPIDEMIOLOGY OF TUBERCULOSIS[1] [2]

GAYLORD W. ANDERSON

(Received for publication May 26, 1952)

If we may define epidemiology as the science of the occurrence of disease, we may then redefine this part of this general session as an examination of the salient facts regarding the occurrence of tuberculosis at the middle of the Twentieth Century. In such an examination we have the dual task of analyzing not only the actual occurrence but also the trends, in the hope that through such an analysis we may gain some insight into the factors underlying these trends and some indication of the direction in which we are proceeding.

Many of the facts regarding the occurrence of tuberculosis are so well known that they need no documentation in a group of this character. Among such are the basic facts of etiology, communicability, relationship to social and economic factors, widespread geographic distribution, and importance. Throughout the centuries, the disease has well merited John Bunyan's epithet as the "captain of the men of death," even though one of the freshmen at the University of Minnesota did write recently in an examination that this was a term applied to the Surgeon General.

The past fifty years have been characterized by a striking decline in tuberculosis. In the United States we have seen the mortality rate of 191 per 100,000 population in 1900 cut to less than half that figure in the first quarter of the century, a further 50 per cent reduction in the ensuing seventeen years, and a second reduction of 50 per cent in the next nine years. In other words, we have witnessed an increasingly rapid rate of decline in tuberculosis mortality, to the point at which the 1951 figure is approximately a tenth of that which prevailed at the turn of the century. This decline has occurred in spite of changes in the registration area which tended to minimize the true rate in the early years of the century.

In examining some of the factors which may be responsible for this increasingly rapid decline in the mortality rate, we should note in particular the changes that have occurred at various age levels. Table 1 and figure 1 portray the rates by

[1] From the School of Public Health, University of Minnesota, Minneapolis, Minnesota.

[2] This address was presented before the Program Development Session as part of the session on *The Tuberculosis Problem Today* at the 48th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, on May 26, 1952.

ages during the period 1910 through 1949 for the registration states of 1900. This chart, which is of a type familiar to all of you, shows the shift in mortality into the older age group, with a virtual elimination of any peak in early adult life. In fact, the sharp increase in rate during adolescence, still apparent in 1940, had all but disappeared by 1949.

These curves suggest that the proportional decline has been greater in the younger than in the older age groups. That this suggestion is a fact is indicated in table 1, which shows the death rates of the registration states by age group and the average annual percentage decline in each interval. The rate of decline is sharper in the younger age groups and this rate of decline becomes progressively

TABLE 1*

TUBERCULOSIS DEATH RATES BY AGE GROUP: 1910–1949
REGISTRATION STATES OF 1900

AGE GROUP	1910	1920	1930	1940	1949	PER CENT DECLINE 1910–1949
Under 5	154	77	36	14	14	90
5–9	31	22	11	3	1.3	96
10–14	63	50	13	5	1.4	98
15–19	132	88	53	20	7.3	94
20–24	177	135	91	38	15	92
25–29	216	157	94	44	19	91
30–34	230	152	89	47	21	91
35–39	232	148	86	48	25	89
40–44	221	141	87	53	31	86
45–49	214	140	91	56	35	84
50–54	203	136	93	65	41	80
55–59	196	134	92	71	46	77
60–64	195	133	92	74	56	71
65–69	194	130	91	73	64	67
70–74	191	126	90	72	53	72
75+	160	98	87	64	51	68

Source: U. S. Bureau of the Census and the Public Health Service, National Office of Vital Statistics.

* Statistical calculations made by Miss Laurel J. Middel, Senior Statistician, School of Public Health, University of Minnesota.

less as age increases. In other words, during the past forty years the reduction in tuberculosis mortality among younger persons has been proportionately greater than in older persons.

This increasingly rapid rate of decline in the tuberculosis death rate is comparable to the decline in typhoid mortality. In the latter disease the initial reduction was occasioned by improvements in sanitation whereby water-borne and milk-borne infections were all but eliminated. There remained, however, a sizable reservoir of carriers who served to spread the disease. Over a period of many years, the number of carriers has decreased as they have disappeared from the community due to natural forces of mortality, and their place has not been

taken by new carriers. Thus, year by year, so long as we have maintained our defenses against typhoid, more carriers have died than have been produced. We have consequently seen the reservoir of infection decrease in size and with it the risk of contracting the disease.

While there is an undoubted hazard in comparisons between an acute infection such as typhoid and a chronic one such as tuberculosis, there is one very obvious similarity. In any disease with a long period of infectiousness for any significant

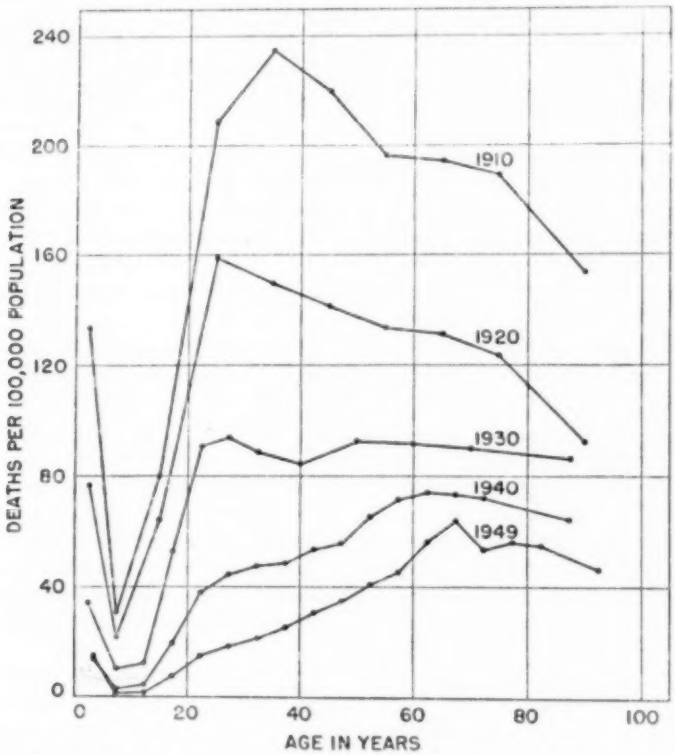


FIG. 1. Tuberculosis mortality rates by ages during the period 1910 through 1949 for the registration states of 1900.

fraction of the cases, the size of the reservoir of chronic cases or carriers depends upon the past history of the disease within the locality in question. A community which has had much typhoid during the preceding forty years will obviously have more carriers than will one which has had little typhoid. An area which has had much leprosy has more sources of infection than one in which leprosy has been all but unknown. So also the community which has had a high tuberculosis disease rate, as reflected by its mortality rate, has obviously more residual sources

of infection than does the community with a low rate. To the extent that the deaths represent a constant fraction of the existing cases, one may interpret the decline in the death rate as reflecting a decline in this reservoir of active cases and, therefore, a reduction in the chances of passing the disease to the non-infected.

If the reservoir of infection is actually becoming smaller, one might logically anticipate that the effect would be manifest in a lowered community infection rate as shown by tuberculin tests and by a greater reduction in death rates among the younger groups than in the older persons.

The decline in infection rates is well known to all of us. For example, only 10.6 per cent of the students entering the University of Minnesota today have positive tuberculin tests as contrasted with 33 per cent of twenty years ago (1). In many of our rural schools the rate today is less than 5 per cent. These data, which can be duplicated in hundreds of other studies, give ample evidence that the decline in death rate is truly paralleled by a decline in infection rate.

The greater decrease in the death rate in the younger groups than in the older groups has already been emphasized. The former, because of their age, must obviously represent persons who have become infected in recent years, whereas persons in the older age groups have lived through periods when the risk of exposure was greater.

All of these observations suggest that in tuberculosis, as in typhoid fever, there is a cumulative effect of our control programs. All measures, such as case finding and hospitalization of patients with open disease, which serve to remove sources of infection from the community must inevitably result in a reduction of exposures which will be reflected in a reduced infection rate and a resultant lowering of the mortality rate in ensuing years. We might logically expect, therefore, the very shifts in age distribution of deaths that we have actually experienced, a shift in mortality into the older age groups and a greater proportional reduction in mortality in the younger age groups. In everyday terms, we are today collecting compound interest on our control programs of former years and we may anticipate that, if we continue our programs, we may pass on to the next generation as rich a heritage as was given to us.

While the cumulative effect of reducing the size of the reservoir has undoubtedly been a factor in the progressively rapid rate of decline in tuberculosis mortality over a long period of years, it cannot satisfactorily explain the sudden drop which has occurred during the past six years.

This period has been marked by a sudden break in the trends which formerly prevailed. The precipitous drop, starting between 1945 and 1948, which has been observed in the United States and Canada has been even more marked in a number of other countries (table 2). Thus, while the rate in the United States fell from 37 in 1945 to 22 in 1950, Canada experienced a decline from 46 to 26, Denmark from 33 to 14, Sweden from 59 to 22, Switzerland from 83 to 35, and Italy from 93 to 40 (2). Countries which ten years ago had rates well above those of the United States, by 1950 had achieved equal or lower rates. Even a country such as the Netherlands, which had experienced a disastrous rise of 100 per cent

in its tuberculosis death rate during the years of Nazi occupation, had reached a 1950 level below that of the United States and less than half that of the prewar years. No period in recorded history has shown a more striking reduction in the mortality rates than have the past seven years.

It would be both presumptuous and hazardous to attempt to formulate a reason for these sudden drops in the tuberculosis death rate until more data are available. Those who believe in BCG vaccine may derive much satisfaction from the fact that the rates in the Scandinavian countries have declined more rapidly than in the United States, and that this decline has been particularly steep in the group under 15 years of age. Yet this simple explanation would hardly explain the comparable drop in my own state of Minnesota, where probably as little BCG has been used as anywhere in the world, and where the total rate has

TABLE 2

TUBERCULOSIS MORTALITY RATES PER 100,000 POPULATION, CLASSIFIED BY COUNTRY: 1930–1950

COUNTRY	1930	1935	1940	1945	1950
United States	71	55	46	37	22
Canada	79	61	51	46	26
Italy	112	89	74	93	40
Netherlands	75	52	44	86	19
Switzerland	125	97	78	83	35
Denmark	71	52	35	33	14
Finland	240	181	212	187	93
Iceland	216	129	86	68	20
Norway	149	106	82	65	29
Sweden	126	94	71	59	22

Source: National Office of Vital Statistics, World Health Organization, and Central Statistical Bureaus of various countries.

declined 50 per cent in five years and the rate under 15 years of age declined some 70 per cent.

Other observers have attributed the decline in large part to improved treatment, which has brought about a reduction in deaths without a comparable reduction in morbidity. Great emphasis is placed upon the fact that there has been no commensurate decline in morbidity rates, and that in some areas these latter rates may have actually increased. While no one would deny the published statistics of newly reported cases, I would question the conclusion that such data prove tuberculosis to be spreading at a greater rate than in former years. The increased tempo in our case-finding programs cannot be eliminated as a factor in maintaining a high case rate.

To my mind it is extremely doubtful if we can truly attribute the decline of the past six or seven years solely to improved methods of treatment. It seems more probable that several factors may be operative and that the dominant forces in one area may well be different from those in another. Thus, in the state of

Minnesota I would suspect that the increasingly rapid decline in the size of the reservoir may well be the chief factor in our sharp reduction during the past half-decade, yet at the same time accord to BCG vaccination a large share of the reduction in certain Scandinavian countries. There is no reason to assume the operation of a universally applicable influence.

Reference has already been made to the shift in age distribution of tuberculosis deaths. This shift has important implications for our control programs and real significance in interpretation of the epidemiology of tuberculosis; yet we must not lose sight of the fact, as emphasized by Merrill (3), that this shift does not reflect any change in the age selectivity of the tubercle bacillus. The hazard of infection in the young adult remains and there is still ample evidence that this period of life is the period of maximum susceptibility.

The true significance of the shift in age distribution lies in the increasing importance of the older age group as a source of infection for the younger generation. Twenty-five years ago emphasis in tuberculosis control programs was being placed upon case finding in children, on the hypothesis that through recognition of the infection in childhood we might avert "breakdown" in adult life or through periodic re-examination detect such "breakdown" in its early stages. Today we have realized that our most profitable case-finding programs lie not in the discovery of the potential victims of future years but rather in the recognition of sources of infection and actual victims of early infection.

Downes (4) has emphasized the importance of family infection as a factor in the perpetuation of tuberculosis and has noted that the infection rate within a family of today may be as great as in former years. If her concept is correct, the chief decline in the tuberculosis mortality rate is due to a reduction in the number of tuberculous households. This concept is in keeping with the idea of a smaller reservoir of infection even though the risk of those exposed to sources of disease is no smaller today than in former years. The concept adds strength to the idea of the importance of the family as the epidemiologic unit in tuberculosis.

Chadwick and Pope (5), here in Massachusetts, have stressed the importance of infection in family contacts and the resultant value of careful epidemiologic investigations as contrasted with indiscriminate surveys in the discovery of infection. Their findings are representative of the results of countless studies in many parts of the world. Today we have overwhelming evidence that the rates of infection and of active disease are many times as high in the family contacts as in the general population. Plunkett (6), in his studies of the cost of various case-finding procedures, has further emphasized the greater importance of the older family contacts as contrasted with the children. He found the highest yield of sources of infection in the adults, and especially in those in the group over 45 years of age. The breakdown rate as shown by the results of repeated examinations showed no variations in the group over 15 years of age but was nil in those under 15.

These studies and many others of a like nature are familiar to all in this group. I would not mention them before an audience of this character did I not believe that in the current wave of enthusiasm for mass roentgenographic surveys we

have tended to lose sight of the true epidemiology of tuberculosis. The mass survey is based on the premise of examining all in the community and makes no discrimination between those who because of known contact have a high risk of infection and those in whom the risk is slight because of absence of such contact. There is no denying the fact that a survey will uncover cases without known contact and will discover households in which unsuspected foci of infection exist, but we must recognize the fact that surveys do not take the place of careful epidemiologic investigation of contacts in the discovery of sources and new infections. If there is one thing that we have learned from the epidemiologic investigations of the past quarter-century, it is the importance of repeated household contact with adults in the spread of infection. It would be unfortunate were we to lose sight of this fundamental epidemiologic factor and so alter our case-finding programs that we fail to place our chief emphasis upon the family contacts among whom the risk is at a maximum.

Yet there are some suggestions that in our programs of control we may be failing to recognize this importance. Thus, among the communities included in the 1947–1948 American Public Health Association studies on administrative practices (7), the median figure for contacts reported per new case fell below the number in the 1943–1944 survey, while the percentage of family contacts actually examined was no greater than that of the earlier survey. Even more serious is the fact that the median percentage of new patients visited by the public health nurse within a month after report declined from 90 to 78 per cent. One may well ask if we are not showing signs of losing sight of the epidemiologic significance of family association.

Before closing this discussion of the epidemiology of tuberculosis, may I insert one further word of warning. I have discussed tuberculosis as though we were dealing with a disease in which the epidemiologic factors were quite constant from one period of time to another or from one place to another. Such is certainly not the case. Probably there is no other infectious disease in which the epidemiology is so variable. This is neither the time nor place to revive the controversy concerning the significance of endogenous versus exogenous reinfection or to speculate on the degree of resistance that goes with a primary infection. From the voluminous discussion of such problems, we have learned that no generalizations can be made which are universally applicable.

In one community with a small reservoir of infection, the risk of endogenous reinfection may well outweigh the risk of exogenous, whereas in another community with a large reservoir, as shown by a high mortality rate over a period of years, the endogenous risk may be insignificant as compared with the high exogenous risk. In the community with small reservoir, a slight reduction in the reservoir size may be highly significant in affecting the likelihood of new infection and therefore every effort may well be directed toward achieving such a reduction. In the other community a sizable numerical reduction may still leave so large a reservoir as to constitute a serious threat. In this latter situation, control measures may be justified which would not be warranted in the community of small exogenous risk.

Thus, a decline in rate attributed to the cumulative effect of reduction in size of an already small reservoir might well parallel an equal reduction achieved through vaccination of young susceptibles in the community with a large reservoir. The very difference in risks of infection in the two communities must be kept constantly before us lest we be led to too hasty generalizations regarding the factors underlying reductions in rates.

In summary: From the above discussion a few facts emerge which are incontrovertible even though differences of opinion may exist as to their significance. The first of these is that tuberculosis mortality is still declining and actually falling more rapidly than ever before in our known history. We may differ in our explanations of this fall, but such differences of opinion do not alter the fact of the decline, which has been sharper in many other countries than in the United States and has brought their rates below ours. The second salient fact is that nothing has arisen to alter our concept of the family as the important epidemiologic unit in the development of tuberculosis and the adult members of the family as the most significant segment, both as sources of infection and as victims. Our control programs, if they are to be soundly conceived and economically conducted, must not lose sight of this fundamental concept.

SUMARIO

Epidemiología de la Tuberculosis

De esta discusión brotan algunos hechos que son incontrovertibles, aun cuando hay discrepancia de opiniones en cuanto a lo que significan. El primero de ellos es que la mortalidad tuberculosa conti bajando y, en efecto, descendiendo más rápidamente que jamás antes en la historia conocida. Podemos discrepar al tratar de explicar esa baja, pero esas diferencias de opinión no alteran el hecho de la baja, que ha sido más aguda en otros muchos países que los Estados Unidos, poniendo sus coeficientes por debajo de los nuestros. El segundo hecho saliente es que no ha surgido nada que modifique nuestro concepto de la familia como la importante unidad epidemiológica en la aparición de la tuberculosis y de los miembros adultos de la familia como segmento más significativo, como focos de infección a la par que como víctimas. Nuestros planes de lucha no deben perder de vista ese concepto fundamental, si van a ser concebidos lógicamente y a ser ejecutados económicamente.

RESUME

Epidémiologie de la tuberculose

Il ressort de cette étude quelques faits qui sont indiscutables, même lorsqu'il existe des différences d'opinion quant à leur signification. Le premier de ces faits est que la mortalité par tuberculose continue à décliner et qu'elle s'abaisse actuellement à un rythme plus rapide qu'à tout autre moment de notre histoire. Nos explications de cette chute peuvent différer, mais ces différences d'opinion ne changent pas le fait que ce déclin a été plus marqué dans beaucoup d'autres pays qu'aux États-Unis et a abaissé leur taux de mortalité au-dessous du nôtre. Le second fait saillant est que, dans le développement de la tuberculose, rien ne s'est produit qui permette de modifier notre conception de la famille comme représentant l'unité épidémiologique importante, les membres adultes de la famille étant la fraction la plus significative, à la fois comme source et comme victimes de l'infection. Ce concept fondamental ne doit pas être perdu de vue dans l'élaboration de nos programmes de lutte contre la tuberculose, s'ils doivent être conçus de façon saine et réalisés économiquement.

REFERENCES

(1) Boynton, R. E.: Personal communication.
(2) Drolet, G. J., and Lowell, A. M.: Whither tuberculosis?, Dis. of Chest, 1952, *21*, 527.
(3) Merrill, M.: Time-specific life tables contrasted with observed survivorship, Biometrics, 1947, *3*, 129.
(4) Downes, J.: How tuberculosis spreads in a rural community, Am. J. Pub. Health, 1936, *26*, 30.
(5) Chadwick, H. D., and Pope, A. S.: The Modern Attack on Tuberculosis, rev. ed., The Commonwealth Fund, New York, 1946.
(6) Plunkett, R. E.: Case-finding: An evaluation of various techniques, Am. Rev. Tuberc., 1939, *39*, 256.
(7) American Public Health Association, Committee on Administrative Practice: Health Practice Indices 1947–1948, New York, 1950.

TUBERCULOSIS IN THE ISLAND OF PUERTO RICO[1]

J. RODRÍGUEZ PASTOR AND JOSÉ L. JANER

(Received for publication July 11, 1952)

INTRODUCTION

Puerto Rico, with its 2,211,000 inhabitants crowded into an area of 3,423 square miles, is at present one of the most densely populated areas in the world, its population density being close to 650 persons per square mile or approximately thirteen times that of continental United States. At the same time, the present ratio of births to deaths in the Island, namely, about four births to each death, gives its population one of the highest growth potentials on record, made evident by a rate of natural increase twice that of continental United States in recent years.

Although it is a rather common tendency in continental United States to consider Puerto Ricans as a racial group entirely different from the main groups which make up the present population of the United States, the 1950 census of the Island's population classified the 2,211,000 inhabitants enumerated as 80 per cent white and 20 per cent non-white (1). The white population consists chiefly of direct descendants from immigrants of western European stock, mostly Spaniards. Because of intermarriage among whites and Negroes, the non-white population of the Island may be considered today as made up chiefly of mulattoes. As a result it has become practically impossible to draw a sharp boundary line between the two racial groups in the sense that is considered possible in some other communities.

It may be added that during the last two centuries there have been practically no Indians among the inhabitants of the Island.

Such a high density and rapid rate of growth of population in a small island with very limited natural resources must be considered among the most important factors contributing to the low standards of living and the socio-economic problems with which Puerto Rico has long been associated. A good example of a problem affected by the rapid increase of population is the housing situation. The housing problem in the Island has been a tremendous one during the last half century, and especially since the first World War when large migrations began from the rural areas to towns and cities. As a result of these migrations, as well as low wages, unemployment, and persistently high birth rates, every town of the Island has one or more large slums where hundreds of shacks are grouped together in a relatively small tract of land, with very meager sanitary facilities. In these slums the families are large, the standards of living low, and the opportunities for the spread of contagious diseases are abundant.

Great efforts have been made by the insular government during the last few years to improve living conditions, especially to solve the housing problem.

[1] From the School of Medicine of the University of Puerto Rico, San Juan, and the Health Department of Puerto Rico.

Some admirable gains have been made, but the task is a huge one and it will be a long time before any great changes in the present situation will be brought about.

An idea of the task ahead may be appreciated if the results of a recent study are considered which estimated that more than 60 per cent of the Island's families are living on incomes too low to cover the amount needed for a minimum adequate diet, with no financial means at all to provide for the other necessities associated with a decent standard of living (2).

Given these conditions of extreme overcrowding, great poverty, and low standards of living, it is not surprising that communicable diseases still constitute in the Island the most important causes of death. Even as recently as 1951, tuberculosis mortality registered in Puerto Rico a rate of 117.8 deaths per 100,000 population. This figure is almost six times the corresponding provisional rate registered in continental United States (20.1) during that same year.

It is interesting, however, that in spite of such adverse conditions the mortality rates from those communicable diseases which have long been associated with the relatively high level of the crude death rate have been declining steadily during the past decade or so (figure 1). Tuberculosis has been no exception to this phenomenon, and its mortality trend reveals a decrease, during the period from 1935 to 1951, comparable to that registered in many states of the United States during the same interval.

TREND OF THE TUBERCULOSIS MORTALITY DURING THE LAST HALF-CENTURY

Death registration in Puerto Rico has been considered reasonably complete for a long time. The customs and religious beliefs of the vast majority of the population, as well as the relative accessibility of cemeteries, have contributed to this high grade of completeness of death registration. Studies made have always served to add support to this assumption. It was no surprise, therefore, that, when the vital statistics system of the Island was centralized in the Insular Health Department, in 1931, the Island was immediately admitted to the United States Death Registration Area although not to the United States Birth Registration Area. It is recognized, however, that, although there has been adequate completeness of death registration in the Island during most of the period covered by the last half-century, the certification of cause of death in the death certificates has suffered from considerable inaccuracies, especially during the first half of this period. This fact introduces limitations in the use of the official statistics on cause of death not to be neglected by any serious student of health problems. However, for the sake of completeness, some of the data on tuberculosis mortality collected by the vital statistics system, even prior to its centralization in 1931, will be presented and analyzed.

The discussions which follow throughout the rest of this paper will help the readers in their appraisal of the relative validity of the figures corresponding to tuberculosis mortality in the Island during the years prior to 1931.

As can be seen from figure 2, the tuberculosis death rate, although already at a very high level, seems to have started to increase at a rather rapid rate in approxi-

mately 1924, when 204.0 deaths from tuberculosis per 100,000 population were recorded, and reached a rate of 261.6 in 1928. In September, 1928, a great hurricane swept the Island and at least 200,000 homes and most of the crops were destroyed. Much privation and suffering followed in the wake of this disaster,

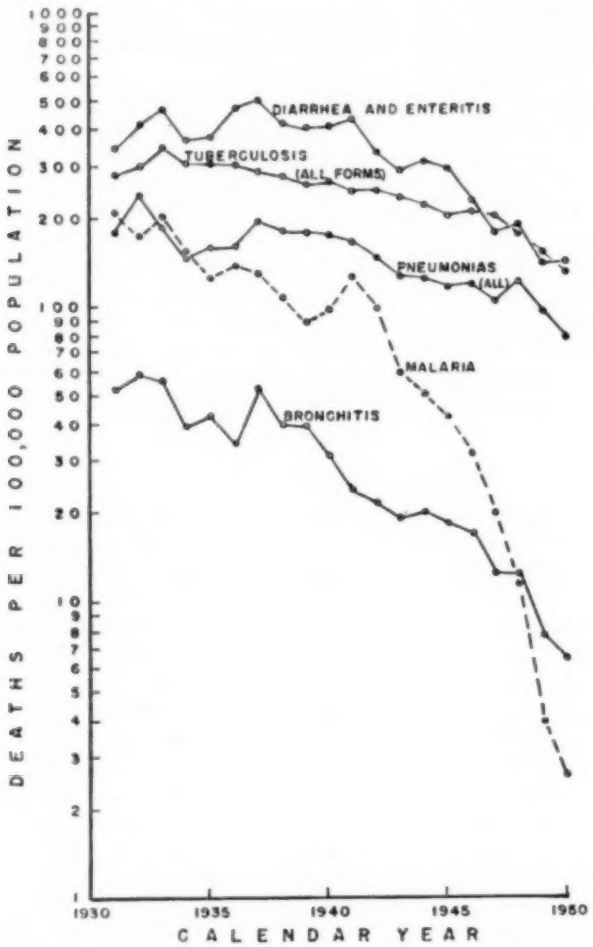


FIG. 1. Mortality from important communicable diseases in Puerto Rico.

and the problem of overcrowding, already acute, became worse. The effect of these calamities became evident almost at once in the tuberculosis mortality, which rose sharply from 261.6 in 1928 to 302.4 in 1929. In 1930 there was a compensatory decline to 262.9, but the upward trend was re-established in the follow-

ing two years, and a rate of 294.4 was reached in 1932. Then, in September, 1932, another great hurricane struck the Island, leaving a trail of destruction almost as large as that of 1928. This calamity contributed to the rise in the tuberculosis mortality rate to the unprecedented level of 332.5 deaths per 100,000 population recorded in the year 1933. Again, a compensatory decrease was observed in the mortality from tuberculosis during the following year, and the rate of 332.5 recorded in 1933 dropped to 302.7 in 1934. This drop was followed by a short period of relative stability and a most remarkable downward trend which has continued uninterruptedly for a period of fifteen years, being especially pronounced during the last four years.

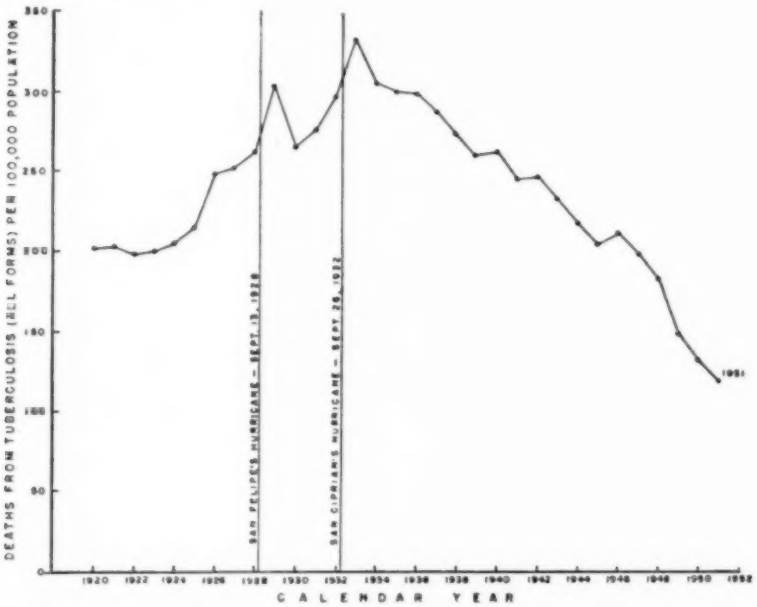


FIG. 2. Mortality from tuberculosis (all forms) in Puerto Rico for the years 1920–1950.

When plotted on a logarithmic scale against the general mortality curve, the trend of tuberculosis mortality in the Island from approximately 1932 on reveals a striking parallel to the trend of mortality from all causes, which suggests the possibility that the increasing trend of the tuberculosis death rate observed in figure 2, starting from the year 1924 and to which reference has already been made, may have been more apparent than real, probably due to improvement in the cause of death certification in the death certificates. This possibility is made even more evident in table 1.

Tuberculosis mortality in Puerto Rico, as elsewhere, has been consistently higher in urban than in rural areas. However, during the period covered since the

TABLE 1

DEATHS AND DEATH RATES FROM ALL CAUSES AND FROM TUBERCULOSIS (ALL FORMS) AND PER CENT OF ALL DEATHS ATTRIBUTED TO TUBERCULOSIS

Puerto Rico, 1915–1950

YEAR	ALL CAUSES		TUBERCULOSIS		PER CENT OF ALL DEATHS ATTRIBUTED TO TUBERCULOSIS
	Deaths	Rate	Deaths	Rate	
1915	25,115	20.7	2,107	173.3	8.4
1916	29,491	23.9	2,389	193.6	8.1
1917	38,675	30.9	2,707	216.0	7.0
1918	38,299	30.1	2,693	211.8	7.0
1919	30,570	23.7	2,393	185.4	7.8
1920	29,918	22.8	2,652	202.2	8.9
1921	30,015	22.5	2,710	203.0	9.0
1922	29,666	21.8	2,706	199.1	9.1
1923	27,143	19.6	2,754	199.2	10.1
1924	27,332	19.4	2,868	204.0	10.5
1925	33,519	23.4	3,237	226.4	9.7
1926	32,946	22.7	3,617	248.9	11.0
1927	30,500	20.7	3,724	252.1	12.2
1928	35,467	23.6	3,925	261.6	11.1
1929	38,534	25.3	4,610	302.4	12.0
1930	28,870	18.6	4,080	262.9	14.1
1931	32,146	20.3	4,338	273.9	13.5
1932	35,610	22.0	4,755	294.4	13.4
1933	36,763	22.3	5,476	332.5	14.9
1934	31,703	18.9	5,082	302.7	16.0
1935	30,753	18.0	5,094	297.8	16.6
1936	34,788	20.0	5,182	297.3	14.9
1937	37,132	20.9	5,091	286.5	13.7
1938	33,870	18.7	4,954	273.6	14.6
1939	32,631	17.7	4,747	257.4	14.5
1940	34,477	18.4	4,886	260.2	14.2
1941	35,551	18.6	4,641	242.7	13.1
1942	32,218	16.6	4,756	244.4	14.8
1943	29,065	14.7	4,572	230.9	15.7
1944	29,843	14.8	4,335	215.2	14.5
1945	28,886	14.1	4,142	202.2	14.3
1946	27,570	13.2	4,317	207.3	15.7
1947	25,411	12.0	4,160	196.5	16.4
1948	26,204	12.2	3,858	179.4	14.7
1949	23,391	10.7	3,205	146.7	13.7
1950	21,917	9.9	2,861	128.9	13.1

centralization of the vital statistics system in 1932, it has been observed that mortality from tuberculosis in Puerto Rico has been declining at a faster rate in the urban areas than in the rural. This can be clearly seen in figure 3.

All of the 77 municipalities which comprise the Island of Puerto Rico have benefited from the downward trend observed in mortality from tuberculosis in Puerto Rico during the last fifteen years. The extent to which each municipality has been able to reduce its death rate from tuberculosis during the last fifteen years is indicated in figure 4.

Although the present writers are aware that the difficulties involved in the classification of the population by race or color, to which reference has already

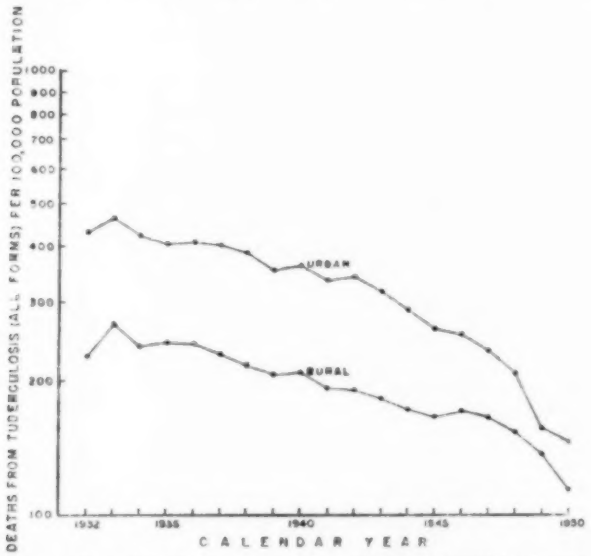
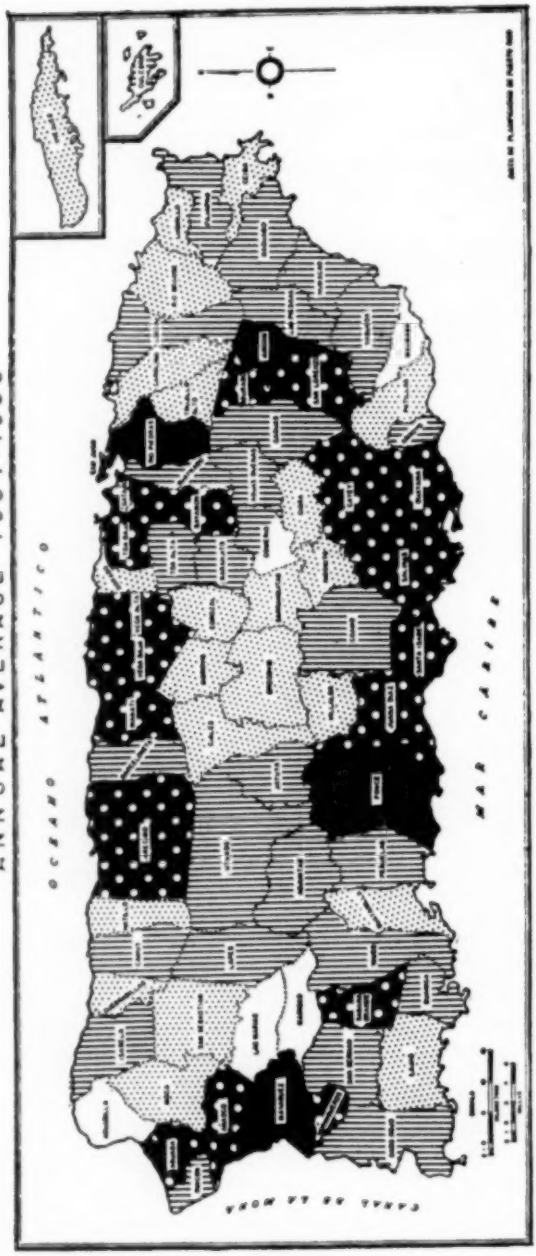


FIG. 3. Urban and rural mortality from tuberculosis (all forms) in Puerto Rico for the years 1932–1950.

been made, must necessarily affect the accuracy of the race-specific statistics, it is interesting to observe that the trends of mortality from tuberculosis among the white and non-white populations as recorded by the Health Department show a decided tendency to converge. That is, the tuberculosis mortality among non-whites, always higher than among the whites, seems to be coming down faster.

TUBERCULOSIS MORTALITY BY AGE AND SEX

In Puerto Rico, as elsewhere, there seems to be no sex selection of tuberculosis mortality in early childhood. As elsewhere also, the influence of sex is clearly revealed only after the age of puberty, when mortality attains and maintains from then on, during a considerable part of the life span, a higher level in females than


ANNUAL AVERAGE 1934-1936
OCEANO ATLANTICO
MAR CARIBE

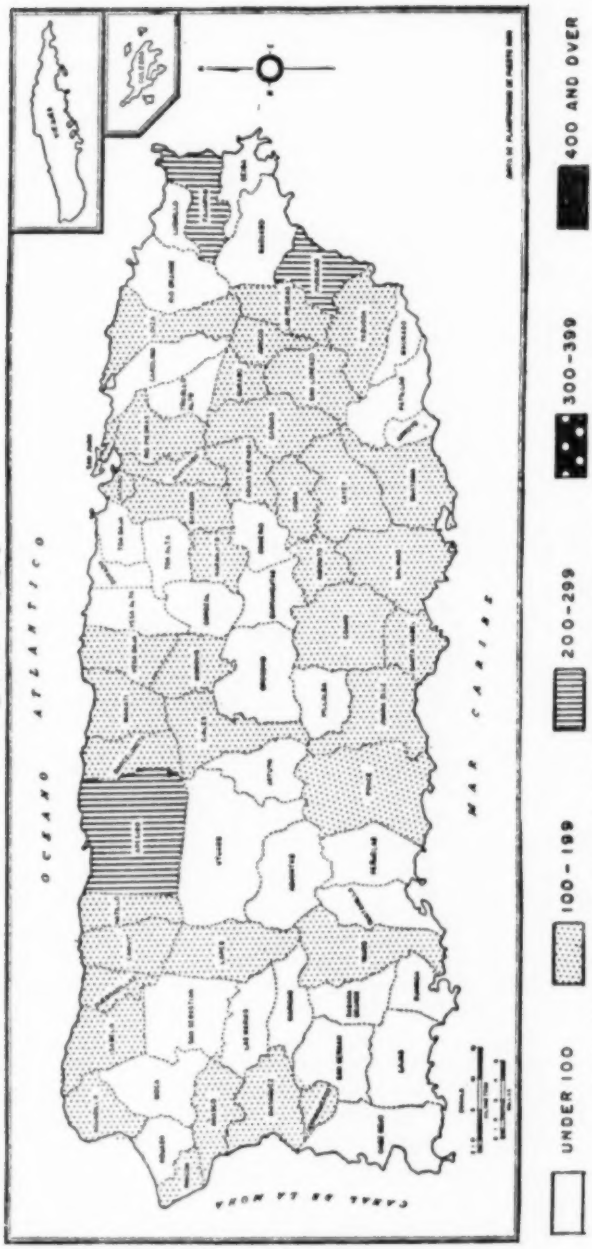


FIG. 4. Mortality from tuberculosis (all forms) per 100,000 population in Puerto Rico by municipalities.

in males. This condition is reversed in the older age groups, but it must be observed (figure 5) that the age at which the situation reverses and mortality becomes higher in males than in females has shifted from the age group forty-five to fifty-four years in 1932 through 1934 to the age group thirty-five to forty-four years in 1948 through 1950. In other words, it seems that, as mortality from tuberculosis decreases in the Island, the reversal of the mortality level of the two sexes tends to occur at a lower age group.

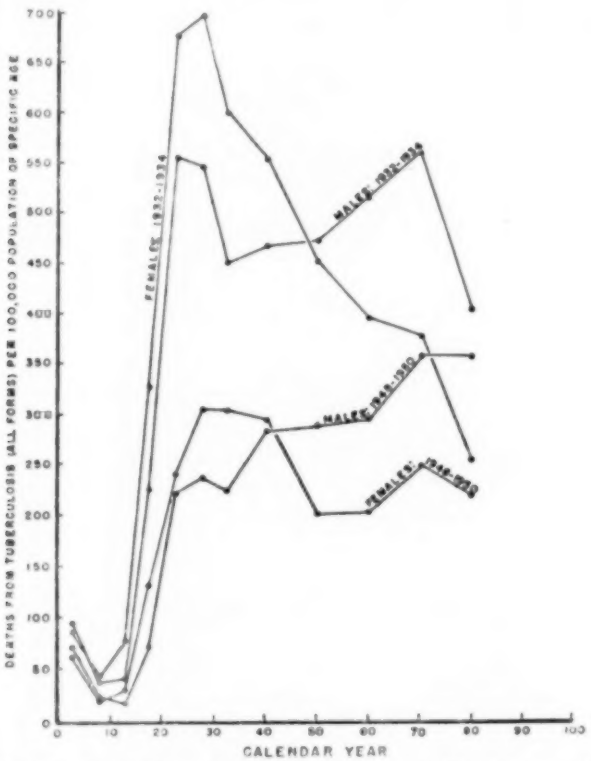


FIG. 5. Mortality from tuberculosis (all forms) in Puerto Rico by age and sex. Annual average for the years 1932–1934 and 1948–1950.

Until the year 1950, tuberculosis mortality in Puerto Rico had been consistently higher among the total female population than among the total male population. Up to the year 1940, the two trends seemed to follow approximately parallel courses. However, from 1940 on the female death rate from tuberculosis began to decline at a faster rate than the corresponding male death rate, and in the year 1950, for the first time in the recorded history of tuberculosis mortality in the Island, the mortality rate from the disease was higher among males than

among females (figure 6). This phenomenon of inversion in the magnitude level of the sex-specific mortality rates from tuberculosis has been observed in other places and has been commented upon by Chadwick and Pope (3), as well as by other writers.

The factors contributing to this change in mortality from tuberculosis by sex are still as obscure in Puerto Rico as elsewhere. Although the population censuses taken during the period do not reveal any great changes in the age structure of the Island's male and female populations, the rates by sex observed during the interval of reference were adjusted for age in order to correct the possible effect of any of the slight changes in age distribution which had actually taken place. This adjustment served only as a confirmation of the fact that the reversal in the magnitude level of the two trends cannot be attributed to the slight changes in the age structure of the male and female population observed during the interval.

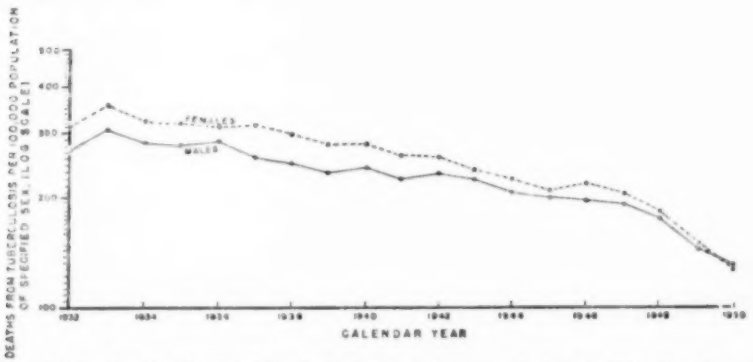


FIG. 6. Death rates from tuberculosis (all forms) by sex in Puerto Rico for the years 1932–1950.

In table 2 is presented the average annual mortality from tuberculosis by age and sex during the two three-year periods 1932 through 1934 and 1948 through 1950, together with the corresponding percentage decreases and male to female death rate ratios.

Although great gains in the reduction of tuberculosis mortality during the sixteen-year interval separating the two periods are observed in every age group of either sex, it can be seen that the greatest relative reductions correspond to the age groups included in the interval between ages five and thirty-four years. It is interesting, however, to notice that the reductions in mortality from tuberculosis in the female groups in the ages between thirty-five and sixty-four years are markedly higher than the reductions observed among the corresponding male groups. This fact must be considered of relative importance in seeking an explanation for the reversal in the magnitude level of the male and female tuberculosis mortality trends which, as already has been said, cannot be attributed to changes in the age structure of the two populations. It suggests the possibility of a rela-

tionship between mortality from tuberculosis and the fertility pattern of the female population, especially with respect to births of the higher orders. However, in studying the fertility pattern of Puerto Rican women by age groups during the years 1940 and 1950, no changes have been found which suggest a causal relationship to the changes in tuberculosis mortality observed during any part of the childbearing period. Therefore, an explanation for this phenomenon must be sought among the more complex factors involved in whatever socio-economic

TABLE 2

AVERAGE ANNUAL MORTALITY FROM TUBERCULOSIS (ALL FORMS), BY AGE AND SEX, IN PUERTO RICO DURING THE TWO THREE-YEAR PERIODS 1932-1934 AND 1948-1950. PER CENT OF DECREASE DURING INTERVAL, AND RATIO OF MALE TO FEMALE DEATH RATES BY AGE GROUP IN EACH THREE-YEAR PERIOD

	MALE DEATHS—TUBERCULOSIS				PER CENT DECREASE IN RATE IN INTERVAL	FEMALE DEATHS—TUBERCULOSIS				PER CENT DECREASE IN RATE IN INTERVAL	RATIO OF MALE TO FEMALE DEATH RATES	
	1932-1934		1948-1950			1932-1934		1948-1950				
	Deaths	Average Annual Rate	Deaths	Average Annual Rate		Deaths	Average Annual Rate	Deaths	Average Annual Rate		1932-1934	1948-1950
1	90	94.7	136	72.0	24.0	75	88.3	87	64.0	27.5	1.07	1.12
1-4	260		257			245		247				
5-9	129	36.4	89	18.9	48.1	134	38.9	87	18.0	53.7	0.94	1.05
10-14	133	41.9	64	16.0	61.8	237	76.9	112	28.3	63.2	0.54	0.56
15-19	624	226.9	221	71.6	68.4	991	327.0	422	131.5	59.8	0.69	0.54
20-24	1,397	557.2	593	222.1	60.1	1,711	676.3	751	240.7	64.4	0.82	0.92
25-29	912	547.0	543	238.2	56.5	1,252	696.5	768	304.8	56.2	0.78	0.78
30-34	655	450.6	463	226.9	49.6	876	597.8	560	306.1	48.8	0.75	0.74
35-44	1,219	467.9	996	283.8	39.3	1,418	553.9	909	294.2	46.9	0.84	0.96
45-54	824	469.5	659	289.1	38.4	705	451.0	494	203.3	54.9	1.04	1.42
55-64	496	515.3	462	296.2	42.5	341	396.0	273	206.8	47.8	1.30	1.43
65-74	255	561.8	292	360.4	35.8	180	376.6	188	250.8	33.4	1.49	1.44
75 and over	84	403.6	129	358.3	11.2	70	255.4	119	220.6	13.6	1.58	1.62
Not stated	—		1			—		2				
All Ages	7,078	285.7	4,905	149.9	47.5	8,235	333.2	5,019	152.8	54.1	0.86	0.98

changes affecting the living and working conditions of the female population may have taken place during the last decade.

FACTORS IN THE DECREASE OF THE TUBERCULOSIS DEATH RATE

The declining trend of the tuberculosis death rate began in Puerto Rico about 1934. There is no doubt that there are several factors which may have influenced this decrease. There is at least one factor, however, which it is believed deserves some discussion at this point, i.e., the influence of the intensive campaign against tuberculosis initiated by the health authorities of the Island in the year 1934.

The very high mortality of 1933 spurred the Island's authorities to renewed

activity in the campaign against tuberculosis. In 1934, due largely to the efforts of Dr. E. Garrido-Morales, Commissioner of Health at that time, one thousand additional beds were made available for "open" cases of tuberculosis, almost tripling the available bed capacity for those cases. At the same time, a very intensive case-finding campaign was launched. Roentgenographic facilities were made available for free chest examinations all over the Island, physicians were trained in the use of the fluoroscope, and laboratory facilities for sputum examinations were greatly increased. As the result of these activities, the number of sputum examinations increased from 6,557 in 1929–1930 to 24,524 in 1934–1935; the number of fluoroscopic examinations of the chest, from none in 1934 to 36,600 in the fiscal year 1936–1937; the roentgenograms taken in dispensaries, from 1,837 in 1934–1935 to 24,700 in 1936–1937. From April, 1935 to July, 1939, 147,000 persons were examined under the new case-finding program. The work done during those four years included 179,540 chest fluoroscopies, 94,435 roentgenograms of the chest, and 125,565 sputum examinations.

At the same time, an effort was made to stop the spread of tubercle bacilli by the use of collapse therapy on as many "open" ambulatory cases as possible and by an extensive house-to-house educational campaign. The effort made in this respect can be judged from the fact that the number of patients under ambulatory pneumothorax treatment increased from 74 in 1934 to 1,962 in 1938–1939. Nineteen fully equipped pneumothorax clinics were organized at strategic points throughout the Island. Much collapse therapy, including surgical collapse, was also done in the new tuberculosis hospitals. In spite of great scarcity of personnel during the second World War and other difficulties, this control program has been continued basically unaltered up to the present time.

Although one cannot tell the extent to which the decline in tuberculosis mortality was influenced by the campaign described above, the coincidence of the two events is certainly interesting. This is especially true in view of the fact that a definite downward trend of the mortality curve had not yet become evident in the years which preceded the campaign.

Concerning the factors that may have brought about the remarkable decline in general mortality which has taken place since 1941, one might point to the organization of milk stations for babies and pre-school children all over the Island since 1933; the training of mothers in infant feeding through these stations; and the relief in unemployment due, first, to the many work projects which were a part of the United States governmental program and, subsequently, to the utilization of man power during World War II. Minimum wage and hour laws and other labor legislation improved working conditions, and the many housing projects of the last few years have helped to ameliorate the awful plight of the hundreds of thousands of slum dwellers. The combined effect of all of these measures, although not enough to bring about spectacular improvement in living conditions, may have been sufficient to prevent thousands of deaths formerly due to extreme misery, ignorance, and neglect, especially among small children.

To the above factors must be added certain public health measures, such as the engineering project for draining marshlands and the extensive use of DDT to

eradicate the *Anopheles* mosquito in those parts of the Island where malaria was most prevalent. These measures resulted in bringing down the death rate from malaria from 141 deaths per 100,000 population in 1941 to 2.0 in 1950. The drinking water supply has been continually improved throughout the Island and hospital facilities, although still very inadequate, have increased considerably since the district hospitals were organized. Another important public health measure was the organization of public health units throughout the Island, with infant, prenatal, and venereal disease clinics, and a wide campaign of public health education through visiting nurses.

And last, but by no means less important, must be mentioned the fact that it was during this period that antimicrobial drugs were made available for widespread use in the fight against disease.

All of these factors, which taken together undoubtedly explain the considerable reduction registered in the general mortality rate of the population during the last decade or so, must have had their share also in the reduction of the mortality rates from tuberculosis during the same period.

INCIDENCE AND PREVALENCE OF TUBERCULOUS INFECTION

Case reporting by private physicians has always been very deficient in the Island. This deficiency is undoubtedly reflected in table 3, which presents on an annual basis and for a number of years: (*a*) the number of deaths attributed to tuberculosis, (*b*) the number of cases of the disease reported to the Health Department by physicians, and (*c*) the ratio of cases to deaths corresponding to each of the years included in the table.

It is therefore very difficult at present to estimate the true incidence of tuberculosis on the Island. However, its prevalence can in some way be roughly estimated by making use of the results obtained in tuberculosis surveys which have been made at different times.

Tuberculin: In 1929, one of the writers applied the intradermic tuberculin test to 2,500 children of eight to ten years of age in several urban and rural schools of the Island. Three successive doses of 0.01 mg., 0.1 mg., and 1 mg. of Old Tuberculin were used. The proportion of reactors was 78.5 per cent in the towns and 57.5 per cent in the country (4).

In 1935, a tuberculin survey made among 4,025 urban dwellers of all ages, using the Mantoux test with Old Tuberculin in doses of 0.1 mg. and 1 mg., disclosed: 38 per cent of positive reactions among children less than five years of age; 66.6 per cent among those between five and nine; 82 per cent among those between the ages of ten and fourteen; 90.6 per cent among those from fifteen to nineteen; and more than 94 per cent in adults older than twenty years of age (5). Another survey made among 1,767 urban dwellers at approximately the same time, using the two strengths of purified protein derivative (PPD) tuberculin, gave an even higher proportion of reactors: 92.6 per cent between the ages of ten and fourteen (6).

In 1941, a tuberculin survey among 1,561 subjects of all ages in an urban municipality (Río Piedras) disclosed: 63.7 per cent of reactors to first- or second-

strength PPD; 53 per cent between the ages of five and nine; 66 per cent from ten to fourteen; 81 per cent from fifteen to nineteen; and more than 90 per cent over the age of twenty. A similar survey in a rural resettlement project (San Just) gave a somewhat lower proportion of reactors at all ages (table 4) (7).

Dr. Robert L. Smith, former Chief of the Bureau of Tuberculosis of the Island Health Department, has given the present writers preliminary figures on the results of extensive tuberculin surveys with PPD made throughout the Island during the past two years in connection with the recent BCG vaccination pro-

TABLE 3

DEATHS ATTRIBUTED TO TUBERCULOSIS (ALL FORMS), NEW CASES OF TUBERCULOSIS REPORTED, AND RATIO OF NEW CASES TO DEATHS IN PUERTO RICO EACH YEAR DURING THE PERIOD 1930-1950

YEAR	DEATHS ATTRIBUTED TO TUBERCULOSIS	NEW CASES OF TUBERCULOSIS REPORTED DURING YEAR	RATIO OF NEW CASES TO EACH DEATH FROM TUBERCULOSIS
1930	4,080	6,688	1.6
1931	4,338	7,302	1.7
1932	4,755	6,346	1.3
1933	5,476	7,599	1.4
1934	5,082	8,302	1.6
1935	5,094	9,559	1.9
1936	5,182	10,339	2.0
1937	5,091	8,871	1.7
1938	4,954	9,420	1.9
1939	4,747	10,158	2.1
1940	4,886	9,238	1.9
1941	4,641	8,564	1.8
1942	4,756	7,670	1.6
1943	4,572	7,158	1.6
1944	4,335	6,699	1.5
1945	4,142	5,761	1.4
1946	4,317	6,318	1.5
1947	4,160	6,472	1.6
1948	3,858	7,287	1.9
1949	3,205	7,231	2.3
1950	2,861	5,866	2.1

gram. Among 90,023 children and adolescents tested between the ages of six and eighteen years, 65 per cent were found to be positive. Among 12,064 children from birth to age six, 19 per cent were reactors. Detailed results according to age distribution are not yet ready, but the above figures are enough to show that the proportion of tuberculin reactors, although probably lower than ten or fifteen years ago (as would be expected from the rapidly decreasing tuberculosis mortality) is still very high.

Roentgenography: In 1934, in a survey of the municipality of Adjuntas, which

covered every other house in the town and every house in a rural district, 2,501 persons were examined. Roentgenograms of the chest were taken of those who gave a history of contact with cases of tuberculosis or showed signs or symptoms of the disease. By this method 30 cases of manifest tuberculosis were found, which were equivalent to 1.1 per cent of the population of the surveyed homes.

A similar survey of the densely populated municipality of Cataño, where every fifth house in the town and every second house in the rural area were visited, revealed 61 cases of tuberculosis among 2,470 persons, a proportion of 2.4 per cent of tuberculosis in relation to the population of the homes surveyed (8).

A tuberculosis survey made in 1941 in the rural resettlement project of St. Just included 3,544 persons, of whom 2,781 (78.5 per cent) had roentgenograms of the chest taken. Manifest tuberculosis was found in 76 (2.7 per cent) of those examined roentgenographically. Eleven (0.4 per cent) showed evidence of pleurisy. Because the figures on the prevalence of tuberculosis in this survey are based on

TABLE 4

PER CENT OF PERSONS REACTING POSITIVELY TO FIRST- OR SECOND-STRENGTH PPD AMONG 2,038 TUBERCULIN TESTED IN A RURAL RESETTLEMENT PROJECT (SAN JUST) AND 1,561 SIMILARLY TESTED IN AN URBAN COMMUNITY (RÍO PIEDRAS), 1941

AGE GROUP	SAN JUST AREA	RÍO PIEDRAS AREA
Total	50.7	63.7
Under 5 years	6.6	22.1
5-9 years	31.8	53.4
10-14 years	55.5	66.1
15-19 years	58.0	81.0
20-29 years	70.4	89.5
30-39 years	77.4	93.5
40 years and over	81.7	97.7

roentgenographic findings, they may be considered more accurate than those in the former surveys, in which only those persons giving a history of contact with cases of tuberculosis or showing symptoms of the disease were examined roentgenographically. These studies suggest that the prevalence of manifest pulmonary tuberculosis in the Island approximately ten years ago was probably more than 2 per cent and that there were at that time no fewer than 36,000 cases of the disease, or approximately 8 or 10 cases for each annual death (7).

During the fiscal year 1949 to 1950, the Bureau of Tuberculosis of the Health Department took photofluorographs of the chest of 234,487 persons, mostly applicants for health certificates and contacts of known cases. Of these fluorographs, 11,009 were found to be "positive" or suspicious of pathology, or deficient, and retakes on them were requested; but only 4,093 persons returned for new repeat roentgenograms. Large films of the chest were taken of these, and among them were found 900 active and 446 probably inactive cases of tuberculo-

sis. The lesions of the active cases were classified as follows: 246 far advanced, 330 moderately advanced, and 324 minimal.

The 1,346 "positive" cases found (including those classed as "inactive") were equivalent to 32.9 per cent of the 4,093 persons who returned for retakes, or to 0.6 per cent of the total of 234,487 persons photofluorographed. Had all retakes requested (11,009) been obtained, using the above findings as a basis, the number of cases of tuberculosis and, therefore, the prevalence of the disease in the total group of 234,487 persons, would have been presumably much lower than in previous surveys.

From the above discussion it seems that both the prevalence and the incidence of cases of tuberculosis in Puerto Rico are now considerably lower among the general population than they were ten years ago. This is in keeping with the marked drop in tuberculosis mortality.

FORMS OF THE DISEASE

Approximately 96 per cent of all tuberculosis deaths are due to pulmonary tuberculosis. Bone and joint tuberculosis are relatively uncommon in the Island, and skin tuberculosis is extremely rare. Erythema nodosum, which some European authorities still consider to be tuberculous in nature, is distinctly rare.

Those pathologists who have had most experience in the study of the forms of tuberculosis which occur in the Island have expressed the opinion that the disease, as seen here in autopsies, presents the same characteristics which are found in similar pathologic material from white American subjects. In 1936, Koppisch, after studying 628 complete and consecutive autopsies on Puerto Ricans, found that the pulmonary changes in persons with tuberculosis were of the ordinary type with caseation and cavitation, and that "there was nothing in the pathological alterations to make of these cases a group by themselves." The upper air passages were found affected only in fatal cases, and so were the gastrointestinal organs. "The pericardium, bones and lymph glands, other than the thoracic, were only exceptionally involved. In only 5 of the 76 non-lethal and healed cases, were lesions noted in the mesenteric lymph nodes." His study of this pathologic material led him to believe that "the anatomical character of the lesions in Puerto Rican whites and mulattoes is no different from that obtaining in well tuberculized peoples." However, of six fatal cases in Negroes, he found two with predominant glandular involvement, two with miliary tuberculosis, and two with fairly extensive tuberculous pneumonia (10).

In 1928, Dr. Alice M. Burke studied and classified the findings in 124 complete autopsies done in general hospitals in Puerto Rico, and compared these with the results of an equal number of autopsies done at the New Haven Hospital in New Haven, Connecticut. From these studies she reached the following conclusion: "Though the series of cases is small, we believe the numbers are sufficient to show that the character of the tuberculosis present in Puerto Rico is much the same as in continental United States, indicating, therefore, a large measure of tuberculization of the people." (11)

Clinicians and radiologists of wide experience find that massive involvement

of lymph nodes, whether in the cervical, submaxillary, or axillary region or in the thorax, is very rarely seen in adults in Puerto Rico.

In New York City, clinicians and pathologists who have studied cases of tuberculosis among Puerto Rican residents have the impression that the forms of the disease which occur in this group are of a more acute character than is generally seen among the white population of the city. They find that the subacute hematogenous forms of the disease are more common among Puerto Ricans.

The experience of clinicians in Puerto Rico points to some difference between the forms of tuberculosis seen in different population groups. Cases coming from the slums run a more rapid course than those coming from districts where living standards are relatively high. This is probably due, more than to anything else, to the abundant opportunities for massive and repeated infections in the slums. Taking into account that most emigrants to New York City come from the poorer classes who usually live in the slums of the Island towns, it is not surprising that, under the strain and stress of life in a large city and in a severe climate, those who have been exposed to heavy infection at home should tend to develop the more severe forms of the disease. The high incidence of tuberculosis among the Puerto Ricans living in New York is not due to lower racial resistance, as has been suggested, but to the fact that these immigrants come to New York from communities where tuberculosis is relatively common and where the opportunities for massive contagion are abundant. A certain proportion of them undoubtedly have the disease, either latent or active, at the time they arrive in New York. The successful fight against tuberculosis in Puerto Rico will be a factor of some importance in helping to solve the tuberculosis problem of New York City, considering that the Puerto Rican population of New York already numbers approximately 400,000 and that the traffic between the city and the Island, especially since the introduction of air travel, is very heavy.

COMMENT

In 1937, Wade Hampton Frost made the following oft-quoted remark:

> However, for the eventual eradication of tuberculosis it is not necessary that transmission be immediately and completely prevented. It is necessary only that the rate of transmission be held permanently below the level at which a given number of infection-spreading (i.e., open) cases succeed in establishing an equivalent number to carry on the succession. If, in successive periods of time, the number of infectious hosts is continuously reduced, the end result of this diminishing ratio, if continued long enough, must be extermination of the tubercle bacillus. (12)

It seems probable that the steady reduction of the number of infectious hosts caused by such control measures as the extensive application of collapse treatment to cases of tuberculosis, intensive case-finding, and the persistent educational campaign have been important factors in bringing about the marked decrease of tuberculosis mortality which has occurred in Puerto Rico during the past fifteen years. There are undoubtedly other causes because, as has already been said, the factors which have contributed to bring down the general mortality

during this period must have affected the tuberculosis mortality as well. Nevertheless, the antituberculosis campaign, which started in 1934 and continued with growing intensity in the following years, must be considered a most important factor in producing and maintaining the declining trend which has been a persistent characteristic of tuberculosis mortality in the Island during the last fifteen years or so.

Streptomycin has been used extensively in the treatment of tuberculosis in Puerto Rico since 1947, and para-aminosalicylic acid has been added to the therapeutic armamentarium since 1949. Although the use of these drugs by general practitioners has not always been wise, there being a tendency to consider them panaceas for every conceivable form of tuberculosis, there is no doubt that their early use has shortened the period of contagiousness in many cases of acute and subacute disease. Moreover, although relapses are common after some time in patients treated with chemotherapy, a certain proportion of the patients have received prolonged benefit, and such results must have helped to bring about the very rapid descent of the tuberculosis mortality curve noticed during the last four years.

A continued decrease in the tuberculosis mortality should be expected in Puerto Rico during the coming years. How fast this decrease will be in the next ten years will depend largely on the continuation and intensification of the well-tested measures of case finding, health education, and the control and isolation of cases of manifest disease. The discovery of a curative drug, which may reasonably be expected in the near future, would certainly be a decisive factor in accelerating the downward trend of the mortality curve. The new drugs, isoniazid and iproniazid, represent an important advance in that direction. In combination with streptomycin, they may bring about a new era of unprecedented achievements in the control of the disease through chemotherapy.

Another control measure has been added recently to those already in use in Puerto Rico, BCG vaccination. Since the application of the vaccine did not start until the last two months of 1949 and its use has been limited to school children of the ages at which manifest tuberculosis is relatively uncommon, the effect of vaccination on the mortality, if any such effect becomes evident, will not begin to show in the vital statistics until a number of years from now. Until the end of 1950, some 50,000 persons of a total population of 2,211,000 had been vaccinated with BCG.

Facilities for the hospitalization of a larger number of "open" cases of tuberculosis will become available with the opening of the new 800-bed tuberculosis hospital in Río Piedras in the latter part of 1952. This modern, excellently planned and equipped institution will bring the total number of beds for patients with tuberculosis in the Island to about 2,300, or roughly one bed for each annual death. More hospital facilities are now being planned for the next few years. The generous help given by the federal government in providing part of the funds for the building of the new hospitals is and will continue to be an important factor in the control of the disease. Likewise of importance is the provision by the United States Veterans Administration of medical services and hospital facilities for

Puerto Rican veterans of the two World Wars who have been afflicted with tuberculosis.

A well-integrated program of rehabilitation for the tuberculous is now being carried on under the auspicies of the Division of Vocational Rehabilitation of the Insular Department of Education, with federal and insular funds. Although the work now being done is excellent, it is limited by the lack of sufficient funds. There is no doubt that more should be done along these lines.

Social and economic reform movements of great importance are now going on in Puerto Rico. One of the most remarkable is the energetic campaign to industrialize the Island. Great efforts are also being made to provide better housing for the low-income groups. Such activities will undoubtedly help to bring down the tuberculosis mortality of the Island to rates more similar to those of the continental United States.

SUMMARY

After having been at a very high level for several years, the tuberculosis mortality in Puerto Rico reached a peak of 332.5 deaths per 100,000 population in 1933. The following year, a new, intensive campaign against tuberculosis was started, based on extensive case finding, ambulatory collapse therapy to open cases, increased facilities for hospitalization, and systematic public health education. The beginning of this campaign coincided with the initiation of a remarkable downward trend of the tuberculosis mortality curve, which has continued without interruption up to the present time. The decrease in tuberculosis mortality in Puerto Rico during those years has proceeded at a rate almost as fast as that observed during the same period in many of the states of the United States. This has happened in spite of the fact that living standards in the Island, although somewhat improved, still remain extremely low for the majority of the population.

The rate of decrease has been more marked since 1947, when streptomycin began to be used extensively in the treatment of the disease.

The use of BCG vaccination did not begin in the Island until October, 1949, and it has been limited chiefly to children of school age, in whom tuberculosis is not very prevalent.

The decline in tuberculosis mortality has proceeded at a faster rate among the female than among the male population. In 1932–1934, tuberculosis mortality was approximately 17 per cent higher for females of all ages than for males. In 1950, although the death rates from tuberculosis had been substantially reduced, the male population (all ages) registered a slightly higher mortality from the disease than the corresponding female group.

When the decline in tuberculosis mortality is studied by age groups, a tendency for the peak mortality from the disease to shift to older age groups in both sexes becomes evident.

Urban-rural and race differentials in mortality from tuberculosis seem to be fading out with the decline in tuberculosis mortality. However, the true meaning of this phenomenon is not clear from the above discussion and will require further and more detailed studies.

In spite of the remarkable decrease in tuberculosis mortality observed in Puerto Rico during the course of the last fifteen years, tuberculosis still alternates with diarrhea and enteritis in the first place among the leading causes of death. Tuberculosis accounts for approximately one-half of all of the deaths which occur in the population among the members of what constitute the most productive age groups in any community, namely, the groups between the ages of fifteen and forty-four.

SUMARIO

La Tuberculosis en la Isla de Puerto Rico

Después de mantenerse a una cifra altísima por varios años, la mortalidad tuberculosa en Puerto Rico alcanzó una cúspide de 332.5 por 100,000 habitantes en 1933. El año siguiente, se inició una nueva e intensa campaña a base de amplio descubrimiento de casos, colapsoterapia ambulante para los casos abiertos, más medios de hospitalización y educación sanitaria sistemática. Los comienzos de esa campaña coincidieron con una notable tendencia descendente de la curva de mortalidad tuberculosa, que ha continuado sin interrupción hasta la fecha actual. La disminución de la mortalidad tuberculosa en esos años ha mostrado casi la misma celeridad que la observada en muchos de los estados de la Unión Americana durante el mismo período de tiempo. Ha sucedido esto, a pesar de que el padrón de vida en la isla, aunque algo mejorado, continúa todavía siendo sumamente bajo para la mayoría de la población.

La tasa del descenso ha sido más pronunciada a partir de 1947, año ese en que comenzó a usarse en gran escala la estreptomicina en el tratamiento de la dolencia.

El uso de la vacunación con BCG no comenzó en la isla hasta octubre de 1949, y se ha limitado en gran parte a niños de edad escolar, en los que no abunda mucho la tuberculosis.

La baja de la mortalidad tuberculosa ha procedido más rápidamente entre la población femenina que entre la masculina. De 1932 a 1934, la mortalidad tuberculosa fué aproximadamente 17 por ciento más alta para las mujeres que para los varones de todas edades. En 1950, aunque los coeficientes de mortalidad tuberculosa habían descendido decididamente, la población masculina (de todas edades) registró una mortalidad ligeramente mayor que el correspondiente grupo femenino.

Al estudiar la baja de la mortalidad tuberculosa por grupos etarios, se pone de manifiesto una tendencia de parte de la mortalidad máxima por la enfermedad a desviarse hacia los grupos de edad más avanzada en ambos sexos.

Las diferencias urbano-rurales y étnicas en la mortalidad tuberculosa se van aparentemente borrando con la baja de dicha mortalidad. Sin embargo, la reseña anterior no acaba de poner en claro el verdadero significado de ese fenómeno, el cual requerirá nuevos y más detenidos estudios.

A pesar de la notable disminución de la mortalidad tuberculosa observada en Puerto Rico en el transcurso de los últimos quince años, la tuberculosis todavía alterna con la diarrea-enteritis en el primer lugar entre las principales causas de muerte, correspondiéndole aproximadamente la mitad de todas las muertes observadas en la población entre los miembros de los que constituyen los grupos más productivos de toda colectividad, a saber, los comprendidos entre las edades de quince y cuarenta y cuatro años.

RESUME

La tuberculose dans l'Ile de Porto Rico

Après avoir été à un niveau très élevé pendant plusieurs années, la mortalité par tuberculose, à Porto-Rico, a atteint un clocher de 332,5 décès pour 100.000 habitants en 1933. L'année suivante, une nouvelle campagne anti-tuberculeuse a été instaurée; elle était fondée sur la recherche extensive des cas de tuberculose, la collapsothérapie ambulatoire pour les cas de tuberculose ouverte et l'enseignement de l'hygiène publique. Le commencement de

cette campagne coïncidait avec le début d'une tendance remarquable à l'abaissement de la courbe de mortalité par tuberculose, qui s'est poursuivi sans interruption jusqu'à maintenant. L'abaissement du taux de la mortalité par tuberculose, à Porto Rico, au cours de ces années a été presqu'aussi rapide que celui qui a été observé dans de nombreux états de l'Union. Ceci s'est produit en dépit du fait que le standard de vie dans l'île, bien qu'amélioré dans une certaine mesure, demeure encore extrêmement bas pour la majorité de la population.

L'abaissement de ce taux a été encore plus marqué depuis 1947, alors que la streptomycine a commencé à être utilisée de façon extensive dans le traitement de cette affection.

La vaccination par le BCG n'a été instaurée dans l'île qu'en octobre 1949 et elle a été principalement limitée aux enfants d'âge scolaire, chez lesquels la tuberculose n'est guère prédominante.

Le déclin de la mortalité par tuberculose s'est poursuivi à une vitesse plus grande parmi la population féminine que parmi la population masculine. Dans la période 1932–1934, la mortalité par tuberculose était approximativement de 17 pour cent plus élevée pour les femmes de tous âges que pour les hommes. En 1950, bien que les taux de mortalité par tuberculose aient été substantiellement réduits, la mortalité par tuberculose a été légèrement plus élevée dans la population masculine (tous âges) que dans le groupe féminin correspondant.

Quand le déclin de la mortalité est étudié par groupes d'âge, on observe, dans les deux sexes, que le clocher de la courbe de mortalité par tuberculose tend à passer aux groupes d'âge plus avancé.

Les taux différentiels de mortalité par tuberculose, urbaine-rurale et raciale, semblent se fondre avec le déclin de la mortalité par tuberculose. Toutefois, la réelle signification de ce phénomène n'est pas éclaircie par l'étude ci-dessus et des études nouvelles et plus détaillées seront nécessaires.

En dépit de la diminution remarquable de la mortalité par tuberculose, observée à Porto Rico au cours des dernières quinze années, la tuberculose partage encore avec la diarrhée et l'entérite la première place parmi les principales causes de décès; elle représente approximativement la moitié de tous les décès qui se sont produits dans la population parmi les membres de ceux qui, économiquement, composent le groupe d'âge le plus productif de toute collectivité, c'est à dire les groupes d'âge de quinze à quarante-quatre ans.

REFERENCES

(1) Bureau of the Census, U. S. Department of Commerce: Characteristics of the Population of Puerto Rico, April 1, 1950. 1950 Census of Population, Preliminary Reports. Series PC-6, No. 12. Washington, D. C., May 27, 1951.

(2) (a) Roberts, L., and Stefani, R. L.: Patterns of Living in Puerto Rican Families: Section I—The Families, Department of Home Economics, The University of Puerto Rico, Río Piedras, P. R., 1949.

(b) Pons, J. A.: Annual Report of the Commissioner of Health of Puerto Rico (1947–1948), page 3.

(3) Chadwick, H. D., and Pope, A. S.: The Modern Attack on Tuberculosis, The Commonwealth Fund, New York, 1946, chapter I.

(4) Crumbine, S. J., Mitchell, H. H., and Tapping, A. P.: Porto Rico, An Inquiry as to the Health of the Children, American Child Health Association, New York, 1930, p. 115.

(5) Rodríguez Pastor, J., Morales Otero, P., Payne, G. C., Ramírez Santos, R., and Silva, E.: Tuberculosis surveys in Puerto Rico, Puerto Rico J. Pub. Health & Trop. Med. 1935, *10*, 514.

(6) Rodríguez Pastor, J.: Tuberculosis in Puerto Rico, Am. Rev. Tuberc., 1937, *35*, 13.

(7) Doull, J. A., Kramer, M., Rodríguez Pastor, J., Arbona, G. and Peterson, J. S.: Pulmonary tuberculosis in a rural tuberculosis community (unpublished report).

(8) Rodríguez Pastor, J., Morales Otero, P., and Payne, G. C.: Tuberculosis surveys in Puerto Rico, Puerto Rico J. Pub. Health & Trop. Med., 1935, *10*, 451.
(9) Annual Report of the Commissioner of Health of Puerto Rico, 1949–1950, p. 58.
(10) Koppisch, E.: Tuberculosis in Puerto Ricans; Review of 628 autopsies, Puerto Rico J. Pub. Health & Trop. Med., 1936, *11*, 492.
(11) Burke, A. M.: Epidemiology of tuberculosis in Puerto Rico: II. Pathological findings in 124 routine autopsies and 1,000 miscellaneous surgical specimens, Puerto Rico J. Pub. Health & Trop. Med., 1928, *4*, 14.
(12) Frost, W. H.: How Much Control of Tuberculosis? Collected papers, edited by Kenneth F. Maxcy, M.D., The Commonwealth Fund, New York, 1941, p. 607.

CARDIOPULMONARY FUNCTION IN THE PULMONARY FORM OF BOECK'S SARCOID AND ITS MODIFICATION BY CORTISONE THERAPY[1, 2]

JOHN H. McCLEMENT[3], ATTILIO D. RENZETTI, AARON HIMMELSTEIN, AND ANDRE COURNAND

(Received for publication July 18, 1952)

INTRODUCTION

Numerous clinical, roentgenographic, and pathologic studies (1–7) of Boeck's sarcoid have established that involvement of the lung is not uncommon and may lead to dyspnea, cyanosis, and even right ventricular failure. Although many observations on pulmonary function in sarcoidosis of the lung have been reported, the physiologic patterns which have been described have been different.

In the earliest report of physiologic studies, Bruce and Wassen (8) demonstrated that a reduction in all of the lung volumes was usually present. Dressler (9) and Leitner (10, 11) confirmed that the vital capacity was usually reduced. In addition, the former found in two cases that the arterial oxygen saturation at rest was normal in one and slightly reduced in the other; the latter found that the maximum breathing capacity could be normal or markedly reduced and that hyperventilation at rest was frequently present. In a study on pulmonary fibrosis, Baldwin and her associates (12) included five patients with Boeck's sarcoid, all of whom had only limited respiratory symptoms and physical findings. Their studies confirmed the earlier findings of reduced lung volumes, reduced maximum breathing capacity, hyperventilation, and normal resting arterial oxygen saturation. Furthermore, physiologic evidence of emphysema was lacking in these cases, and significant arterial oxygen unsaturation did not appear during exercise. From these data it was concluded that mild ventilatory insufficiency without significant disturbance of gas exchange was characteristic of Boeck's sarcoid. In their studies of single patients with pulmonary sarcoidosis, Galdston and associates (13) and Wright and Filley (14) reported similar findings. In addition, Galdston and co-workers, making use of the new methods for the study of pulmonary gas exchange and pulmonary gas distribution developed by Riley, Donald, and Cournand (15, 16), found a slight increase in the physiologic dead space, while the venous admixture in the arterial blood and the calculated oxygen diffusing capacity of the lung were normal.

A second pattern of pulmonary dysfunction in pulmonary sarcoidosis has been described by Austrian and his co-workers (17). In their report of a syndrome

[1] From the Department of Medicine, Columbia University, College of Physicians and Surgeons; and the Cardio-Pulmonary Laboratory of the First Medical and Chest Services (Columbia University Division), Bellevue Hospital, New York, New York.

[2] This investigation was supported (in part) by a research grant from the National Heart Institute of the National Institutes of Health, Public Health Service; and (in part) by a grant from the Life Insurance Medical Research Fund.

[3] James Alexander Miller Research Fellow.

characterized physiologically by an interference with the diffusion of oxygen across the alveolar-capillary septa, and pathologically by involvement of these septa, they included two cases of pulmonary sarcoidosis. Hemodynamic studies revealed some pulmonary hypertension at rest in one of these cases and only during exercise in the other.

A third pattern has been observed by Coates and Comroe (18) and by Lukas (19), both of whom report physiologic changes in pulmonary sarcoidosis consistent with the presence of chronic pulmonary emphysema.

Numerous reports have been published concerning the favorable effect of cortisone and corticotropin (ACTH) therapy upon the clinical and chest roentgenographic findings (13, 19–24). In some of these reports, demonstration was made of a change from a predominantly granulomatous process to a fibrous one in the biopsied lesions (13, 20, 24). Measurements of pulmonary function were included in some of these studies. After nine days of cortisone treatment, Galdston's patient showed a slight increase in vital capacity, total capacity, and maximum breathing capacity (13), a return of the physiologic dead space to normal, and continued hyperventilation at rest. In a patient with the pattern of chronic pulmonary emphysema, Lukas observed a reduction of cough, wheezing, and dyspnea after the start of cortisone therapy. The physiologic studies showed an increase in the vital capacity and maximum breathing capacity, a reduction in the residual volume to total capacity ratio, and a return to normal of the arterial oxygen saturation both at rest and during exercise. In four patients presented by Small (23), a slight to moderate improvement in the vital capacity and maximum breathing capacity was found during or after cortisone treatment.

It is the purpose of the present communication to report 10 additional cases of pulmonary sarcoidosis with pulmonary and cardiocirculatory physiologic measurements; to describe and discuss the physiologic patterns which may occur in this disease; and to discuss the effects of cortisone therapy upon the 5 patients of this group who were treated.

MATERIAL AND METHODS

Methods: Measurements of lung volume, maximum breathing capacity, index of intrapulmonary mixing, ventilation, arterial oxygen saturation, and arterial carbon dioxide tension were made according to the methods described by Baldwin, Cournand, and Richards (25). The partial pressure of oxygen in the arterial blood was obtained by the direct technique of Riley, Proemmel, and Franke (26). Sampling of mixed venous blood and determination of cardiac output were carried out by methods previously reported (27), and blood pressures in the pulmonary and brachial arteries were recorded with the use of Hamilton optical manometers or strain gauge electromanometer.

Analysis of the ventilation-perfusion relationships and of the diffusion characteristics of the lung was made according to the methods described by Riley, Cournand, and others (15, 16). The results of this analysis are expressed as dead space ventilations, venous admixture in the arterial blood, and the oxygen diffusing capacity of the lung. The theoretical considerations upon which this analysis is based, the details of techniques and of calculations, and the errors involved have been discussed elsewhere (15, 16, 28).

Material for study: In all but one of the 10 patients, the presumptive clinical diagnosis of sarcoidosis was confirmed by biopsy of lymph nodes, skin, or liver. Patients were included in this study only if a significant involvement of the lung parenchyma was demonstrated

by roentgenograms of the chest. Repeated biopsies of suitable material were obtained from 4 patients during treatment with cortisone. Vital statistics and clinical data are summarized in table 1.

RESULTS

The results of physiologic studies before, during, and after cortisone therapy are given in tables 2 through 5.

From the observations made before treatment, three distinct types of pulmonary functional abnormality may be identified.

In the first, reduction of lung volumes is associated with mild hyperventilation and sometimes with a minimal degree of ventilatory insufficiency.

In the second, a reduction of lung volumes is associated with disturbances in alveolar-capillary gas exchange characteristic of the syndrome of alveolar-capillary block.

In the third, represented by a single case, the lung volume measurements are consistent with the diagnosis of chronic pulmonary emphysema, and significant disturbances in the ventilation-perfusion relationship and in the oxygen diffusing capacity of the lung are present.

Type 1

Cases 1 through 4 in the present study are representative of this type, which is characterized physiologically by: (*a*) reduction of all lung volumes, usually with a normal residual volume to total capacity ratio; (*b*) normal index of intrapulmonary mixing; (*c*) normal or slightly reduced maximum breathing capacity; (*d*) mild hyperventilation at rest and during recovery from exercise; (*e*) normal arterial oxygen saturation at rest and normal or slightly reduced values after exercise; (*f*) normal oxygen diffusing capacity; (*g*) normal or minor abnormalities of the ventilation-perfusion characteristics; (*h*) mild pulmonary arterial hypertension.

The clinical findings of Case 4 illustrate the first type of pattern.

Case 4. H. B., a 23-year-old Negro, was admitted to Bellevue Hospital on November 14, 1949. Three weeks before admission he developed rhinorrhea headache, chilly sensations, and a temperature of 100° to 102°F. These symptoms disappeared after approximately ten days, but he then developed a nonproductive cough and left anterior chest pain. At the time of admission, an eight-pound weight loss had occurred. He was said to have had a normal chest roentgenogram in January, 1948.

On admission, the patient was afebrile. There was generalized, slight enlargement of the superficial lymph nodes, which were discrete and firm. A lichenoid skin eruption was present. A few fine rales were heard over the lower third of both lungs posteriorly.

A roentgenogram of the chest (figure 1) showed large irregular areas of density in the lower two-thirds of both lung fields. In the upper lung field, similar but smaller densities were present. No tubercle bacilli were found in many specimens of sputum which were examined by smear and culture. A tuberculin skin test was positive. Coccidioidin and histoplasmin skin tests were negative.

During the first month of hospitalization, the patient had a daily temperature between 100° and 101°F. For the remainder of his six months' hospital stay he was afebrile. The

TABLE 1

PHYSICAL CHARACTERISTICS AND CLINICAL DATA IN 10 CASES OF PULMONARY SARCOIDOSIS

CASE	AGE	SEX	HEIGHT	BS AREA m^2	PROBABLE DURATION OF ILLNESS	CLINICAL DATA
	years		*cm.*		*months*	
1. R. S.	32	M	174	1.84	4	Mild cough; no dyspnea; generalized peripheral lymph node enlargement; lymph node biopsy. Chest roentgenogram: diffuse reticular infiltration and hilar adenopathy.
2. T. P.	17	M	171	1.71	24	No dyspnea or cough; generalized peripheral lymph node enlargement and subcutaneous mass on upper lip; skin biopsy. Chest roentgenogram: diffuse nodular infiltration and hilar adenopathy.
3. J. B.	21	M	166	1.68	12	Cough and slight exertional dyspnea; generalized lymph node enlargement; tuberculin test negative. Chest roentgenogram: bilateral patchy infiltration.
4. H. B.	23	M	173	1.70	1	Illustrative case, reported in detail in text.
5. R. B.	23	F	159	1.48	18	Parotid and lacrimal gland enlargement; papular skin eruption; biopsy of mass in left breast. Chest roentgenogram: hilar lymphadenopathy, diffuse linear infiltrations with some bullae.
6. C. L.	21	M	179	1.74	1	Illustrative case, reported in detail in text.
7. W. H.	22	M	183	1.89	12	Cough, dyspnea on exertion, and weight loss; bilateral iritis and generalized lymph node enlargement; biopsy of lymph node. Chest roentgenogram: enlarged hilar lymph nodes, diffuse fine infiltration. Roentgenogram of hand: cystic area in phalanx.
8. L. W.	19	F	155	1.38	60	Illustrative case, reported in detail in text.
9. Q. G.	43	F	156	1.69	36	Cough, severe dyspnea on exertion. Tachypnea, cyanosis, and clubbing of fingers. Liver biopsy. Chest roentgenogram: diffuse linear and nodular infiltrations.
10. P. B.	42	F	169	1.48	More than 48	Illustrative case, reported in detail in text.

chest roentgenogram showed gradual but incomplete clearing. A biopsy of a skin lesion showed a granulomatous lesion characteristic of Boeck's sarcoid.

Type 2

Cases 5 through 9 are representative of this type, which is characterized physiologically by: (*a*) reduction of the lung volume with normal residual volume to total capacity ratio; (*b*) normal index of intrapulmonary mixing; (*c*) well-maintained maximum breathing capacity; (*d*) marked hyperventilation at rest

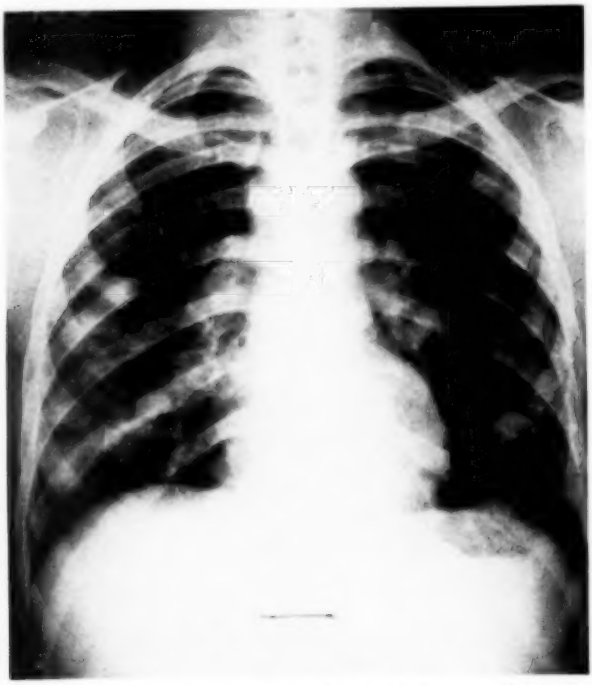


FIG. 1. *Case 4.* Nodular infiltrations throughout both lungs predominate in the lower half of the chest.

and during exercise; (*e*) normal or slightly reduced arterial oxygen saturation at rest and a considerable degree of unsaturation on exercise; (*f*) reduced oxygen diffusing capacity; (*g*) variable disturbances in the ventilation-perfusion relationships; (*h*) pulmonary arterial hypertension.

All but one of the patients in this group were treated with cortisone. Two of these showed definite and significant improvement in pulmonary function. This was manifested chiefly by the return of the oxygen diffusing capacity of the lung to normal. Improvement was also indicated by an increase in the vital capacity and maximum breathing capacity and by decreases in the residual volume and

the degree of hyperventilation. In 2 patients, the pulmonary arterial pressure, after treatment with cortisone, was at a nearly normal level, both at rest and during moderate exercise. The remaining 2 patients with this pattern who were treated showed no definite evidence of physiologic improvement.

The case records of 2 patients of this type are presented in detail:

Case 6. C. L., a 21 year-old Negro, was admitted to Bellevue Hospital on December 7, 1951. He dated the beginning of his illness three weeks prior to admission, when he had the sudden onset of dyspnea after climbing one flight of stairs. This symptom persisted and became associated with a cough productive of small amounts of whitish, occasionally blood streaked sputum, mild left lower nonpleuritic chest pain, and anorexia. During the three months before admission, a twenty-pound weight loss had occurred. He had had no previous significant illnesses, and no history of exposure to toxic substances could be elicited.

On admission, he appeared to be a healthy, but tachypneic young man who preferred the sitting position. He had no fever or tachycardia, and the blood pressure was normal. Fine rales were heard at both lung bases.

Repeated examinations of the sputum failed to demonstrate tubercle bacilli. The tuberculin skin test was negative. A total protein of 8.2 gm. per 100 ml. with an albumin: globulin ratio of 4.8:3.4 was present. A roentgenogram of the chest (figure 2*A*) showed abundant, fine, nodular infiltrations throughout both lungs. In many areas, larger, irregular, confluent shadows were also present. The hilar lymph nodes were enlarged.

An aspiration biopsy of the liver showed many epithelioid granulomata. These lesions contained epithelioid cells, fibroblasts, a few lymphocytes, and an occasional Langhans' giant cell. Histologically, the lesion was characteristic of Boeck's sarcoid.

On January 21, 1952, he was started on daily intramuscular cortisone therapy in dosage of 300 mg. per day. This was reduced to 200 mg. per day three days later. After January 30, cortisone was administered by the oral route. On February 5, cortisone was reduced to 100 mg. per day. Within three days after the start of therapy, his respiratory symptoms had decreased and rales could no longer be heard in the lungs. This improvement continued through March 13, when he was discharged to clinic to continue on 100 mg. per day of cortisone. During this period, his chest roentgenogram showed rapid and steady clearing until it was nearly normal (figure 2*B*) at the time he was discharged from the hospital.

Physiologic studies (tables 2 through 5) before cortisone therapy showed a marked reduction of the lung volumes and maximum breathing capacity, hyperventilation, a marked fall in the arterial oxygen saturation after exercise, a low oxygen diffusing capacity, an elevated percentage of venous admixture in the arterial blood, and pulmonary arterial hypertension during mild exercise. After cortisone therapy, all lung volumes were increased; the hyperventilation had decreased slightly; and the arterial oxygen saturation after exercise, the oxygen diffusing capacity, and the percentage of venous admixture in the arterial blood had all returned to normal.

In summary, this patient is an example of pulmonary sarcoidosis which had resulted in an impairment of alveolar-capillary diffusion. The physiologic and clinical findings both indicated a serious derangement in pulmonary function. He responded promptly and excellently to cortisone therapy, and it seems possible that this satisfactory response was related to the acute evolution of his granulomatous disease.

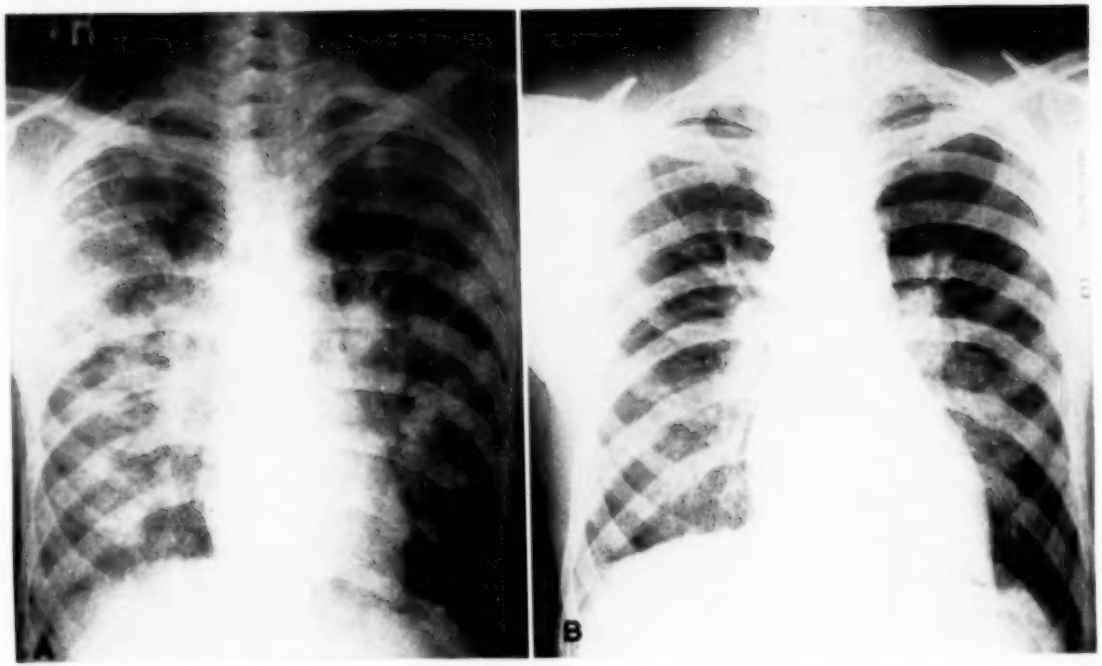


FIG. 2. *Case 6*

A. Before cortisone therapy. Throughout both lung fields there are very numerous, irregular, and confluent infiltrations.

B. After cortisone therapy. The infiltrations have resolved and the chest roentgenogram is nearly normal.

Case 8. L. W., a 19 year old Negress, was admitted to Bellevue Hospital on August 11, 1950. Five years before admission, she noted the insidious onset of malaise, easy fatigability, weakness, a chronic nonproductive cough, and dyspnea on exertion. Shortly after the onset of these symptoms, raised nodular lesions appeared over the skin of the nose and cheeks. These lesions remained unchanged, but the cough and dyspnea progressively increased in the year before admission. She had lost approximately twenty pounds in the year before coming to the hospital.

TABLE 2

LUNG VOLUMES, INDEX OF INTRAPULMONARY MIXING, AND MAXIMUM BREATHING CAPACITY IN 10 CASES OF PULMONARY SARCOIDOSIS

CASE	TIME OF STUDY	VITAL CAPACITY PER CENT PREDICTED	RESIDUAL VOLUME PER CENT PREDICTED	TOTAL LUNG CAPACITY PER CENT PREDICTED	RESIDUAL VOLUME / TOTAL CAPACITY × 100	MAXIMUM BREATHING CAPACITY PER CENT PREDICTED	INDEX OF INTRAPULMONARY MIXING
Normal		100	100	100	<35	100	<2.5
1. R. S.		43	64	50	25	90	1.4
2. T. P.		59	96	64	27	69	1.9
3. J. B.		81	56	77	15	95	1.5
4. H. B.		76	68	81	16	103	0.8
5. R. B.		43	66	50	35	93	1.6
6. C. L.	Before therapy	43	60	46	26	55	1.0
	After 4 weeks of therapy	61	52	60	17	59	1.0
7. W. H.	Before therapy	68	104	78	27	77	0.9
	After 4 weeks of therapy	79	63	76	17	101	1.5
8. L. W.	Before therapy	32*	63	38*	44*	67	1.0
	After 9 weeks of therapy	61	42	56	19	89	0.5
9. Q. G.	Before therapy	49	78	56	36	100	1.3
	After 3 weeks of therapy	57	90	66	35	107	1.1
10. P. B.	Before therapy	55	278	112	64	54	3.4
	After 4 weeks of therapy	62	177	95	48	56	1.4
	Nine months later	52	169	84	48	43	2.0
	After 3 weeks of therapy	58	183	90	53	56	2.0

* Poor cooperation was obtained in determining the vital capacity.

Examination revealed a chronically ill, young, afebrile, Negro woman. There were several discrete, elevated, flat nonulcerated reddish-brown nodules, which varied in diameter from 0.5 to 1 cm., scattered on the cheeks and alae nasae. All the peripheral lymph nodes were enlarged to approximately 1 cm. in diameter and were firm, discrete, and nontender. A few scattered rhonchi were heard in the lungs. The chest roentgenogram (figure 3) showed enlargement bilaterally of the hilar shadows, and a diffuse, fine, miliary-like infiltration throughout both lung fields. A roentgenogram of the hands showed multiple cystic changes in the distal ends of the intermediate phalanges. Tubercle bacilli could not be found in the sputum by smear or culture. The tuberculin skin test was negative. The total

protein of the blood was 9.2 gm. per 100 ml., with an albumin globulin ratio of 4.2:5.0. Biopsies of the skin of the nose and of a cervical lymph node both showed a non necrotic granulomatous lesion characteristic of Boeck's sarcoid. The patient's clinical condition remained unchanged until November 20, 1950, when cortisone therapy was started. She received 100 mg. per day until January 7, 1951, when it was decreased to 50 mg. per day until it was stopped on January 24, 1951. During the course of this treatment, the patient had a marked improvement with a gain of seventeen pounds and a regression of the skin lesions but no definite roentgenographic clearing of the pulmonary process. Biopsies of one of the skin nodules and another cervical lymph node were done on January 15, 1951, and showed that the granulomatous lesions had been largely replaced by fibrous and hyalin

TABLE 3

VENTILATION AND RESPIRATORY GAS IN THE ARTERIAL BLOOD IN 10 CASES OF PULMONARY SARCOIDOSIS

CASE	TIME OF STUDY	VENTILATION L/min./m²		ARTERIAL BLOOD		
				OXYGEN SATURATION		$\dot{Q}/\dot{V}$
		Rest	Exercise	Rest	Recovery	
				per cent	*per cent*	*mm.Hg*
Normal		3.4	10.6	98	98	39
1. R. S.		5.5	10.5	94	94	34
2. T. P.		4.8	14.5	95	93	37
3. J. B.		4.0	9.6	96	90	43
4. A. B.		5.0	15.8	96	98	34
5. R. B.		6.6	10.1	94	—	35
6. C. L.	Before therapy	6.6	14.4	94	81	40
	After 4 weeks of therapy	5.7	—	99	95	33
7. W. A.	Before therapy	5.3	12.0	95	89	33
	After 3 days of therapy	4.6	—	98	96	36
	After 4 weeks of therapy	4.5	7.9	96	93	35
8. L. W.	Before therapy	7.1	14.7	96	74	40
	After 9 weeks of therapy	6.3	16.7	94	75	33
9. Q. G.	Before therapy	5.4	11.4	92	61	39
	After 3 weeks of therapy	6.2	15.9	88	57	40
10. P. B.	Before therapy	8.8	—	85	—	42
	After 4 weeks of therapy	7.4	—	97	—	36
	9 months later	7.4	—	87	74	35
	After 3 weeks of therapy	8.8	15.8	93	76	37

tissue. The feeling of well being experienced by the patient during the cortisone therapy was sustained after its cessation and persisted until she was last seen in April, 1951.

Physiologic findings (tables 2 through 5) before treatment with cortisone were similar to those in the preceding case. Unlike the preceding case, however, the changes which occurred during cortisone treatment were slight and cannot be regarded as significant.

The lack of physiologic response to cortisone therapy is particularly interesting when one considers the histologic change from a granulomatous to a fibrotic process which was found in the skin and lymph node biopsies of this case.

Type 3

Only one case in the present study is representative of this type. Therefore, the clinical and physiologic findings and the effect of treatment upon these will be presented in detail.

TABLE 4

MEASUREMENT OF VENTILATION PERFUSION RELATIONSHIP AND OXYGEN DIFFUSING CAPACITY IN 10 CASES OF PULMONARY SARCOIDOSIS

CASE	TIME OF STUDY	DEAD SPACE VENTILATION IN PER CENT OF TOTAL VENTILATION	ALVEOLAR pO_2 ROOM AIR	A-A GRADIENT AT 2 LEVELS OF OXYGEN		OXYGEN DIFFUSING CAPACITY OF THE LUNG (D_{LO_2})	VENOUS ADMIXTURE IN PER CENT OF CARDIAC OUTPUT
				Room Air	Low O_2*		
			mm.Hg	*mm.Hg*	*mm.Hg*		
Normal		<30	100	12	12	15	<6
1. R. S.		23	114	18	4	>14	<10
2. T. P.		32	104	19	6		
3. J. B.		24	103	14	5	>23	8
4. H. B.		20	116	29	7		
5. R. B.		36	108	26	23	7	12
6. C. L.	Before therapy	40	110	35	28	8	16
	After 4 weeks of therapy	32	113	10	3	18	3
7. W. H.	Before therapy	24	104	20	23		
	After 3 days of therapy	22	108	16	3	32	8
	After 4 weeks of therapy	16	110	19	7	—	—
8. L. W.	Before therapy	44	111	34	29	7	13
	After 9 weeks of therapy	32	114	29	27	5	9
9. Q. G.	Before therapy	39	107	51	49	4	20
	After 3 weeks of therapy	40	106	35	30	5	13
10. P. B.	Before therapy	58	103	40	37†	6	12
	After 4 weeks of therapy	42	112	28	30	5	6
	Nine months later	47	106	51	46	5	22
	After 3 weeks of therapy	46	112	30	40	—	2

* 16 per cent oxygen
† 17.4 per cent oxygen

Case 10. P. B., a 42 year old Negress, entered Bellevue Hospital on December 26, 1950. Four years before admission, a routine roentgenogram of the chest had shown bilateral and widespread pulmonary infiltrations. An enlarged liver and spleen were noted at this time but, because the patient had no significant symptoms, she did not submit to a complete clinical evaluation. Five months before admission, mild dyspnea on exertion was first

noted. This steadily increased in severity until incapacitating dyspnea was present even at rest. In the two weeks before admission, she had chilly sensations and fever.

On admission, she was acutely ill, severely dyspneic and cyanotic. Her temperature was 104° F.; pulse, 140; arterial pressure, 115 systolic, 85 diastolic in mm. of mercury. The

TABLE 5

HEMODYNAMIC MEASUREMENTS IN 8 CASES WITH PULMONARY SARCOIDOSIS

CASE	TIME OF STUDY	PULSE RATE	OXYGEN CONSUMPTION	ARTERIAL-VENOUS OXYGEN DIFFERENCE	CARDIAC INDEX	PULMONARY ARTERY		SYSTEMIC ARTERY	
						s/d†	m‡	s/d	m
			cc./min./m²	*cc./L.*	*l./min./m²*	*mm.Hg*	*mm.Hg*	*mm.Hg*	*mm.Hg*
Normal	Rest	—	126	39	3.3	20/9	13	112/65	84
1. R. S.		97	142	38	3.7	35/11	24	141/88	110
		(120)	(314)	(65)	(4.8)	(41/16)	(29)	(161/95)	(123)
3. J. B.		86	—*	—*	—*	25/12	17	150/97	123
		(100)	(290)	(56)	(5.2)	(32/14)	(21)	(165/101)	(127)
5. R. B.		111	—	—	—	27/10	16	—	—
6. C. L.	Before therapy	104	168	53	3.2	32/13	21	132/77	98
		(100)	(220)	(60)	(3.7)	(41/15)	(28)	(143/79)	(97)
	After 4 weeks of therapy	64	133	44	3.0	27/15	19	141/82	104
7. W. H.	After 3 days of therapy	73	169	35	4.8	16/8	12	122/80	98
		(120)	(516)	(63)	(8.2)	(21/17)	(20)	(134/84)	(101)
8. L. W.	Before therapy	110	165	41	3.6	34/15	24	—	—
	After 9 weeks of therapy	82	121	46	2.7	37/17	26	115/84	99
9. Q. G.	Before therapy	100	146	43	3.4	58/25	39	112/66	85
	After 3 weeks of therapy	109	158	38	4.2	51/16	34	109/68	85
10. P. B.	Before therapy	100	187	60	3.1	54/24	35	95/71	84
	After 4 weeks of therapy	85	156	51	3.1	59/27	37	170/105	131
	9 months later	95	143	46	3.1	45/21	32	92/68	78

( ) Figures in parentheses represent exercise data obtained during "steady state" exercise.

* Measurement of cardiac output at rest technically unsatisfactory.

† s/d = systolic; diastolic.

‡ m = mean.

breath sounds were diminished, many wheezes and rhonchi were heard, and fine rales were present in the lower part of both lungs. The liver was enlarged to below the umbilicus; the spleen, to the iliac crest.

A roentgenogram of the chest showed widespread, dense infiltration and emphysematous bullae throughout both lungs. The initial laboratory study was unremarkable. The acute

febrile episode responded quickly to antimicrobial therapy, and there was slight improvement in her dyspnea. Approximately three weeks after admission, a left sided spontaneous pneumothorax developed. After re-expansion of the lung, it was found that the roentgenographic findings in the chest (figure 4A) were unchanged from admission. Several sputum examinations were negative for tubercle bacilli by smear and culture. The tuberculin test was positive. Mild hypochromic anemia was present and, on one occasion, an eosinophilia of 11 per cent was noted. Hyperglobulinemia and a strongly positive cephalin flocculation were consistently present. Slight albuminuria was always present. A liver biopsy showed scattered epithelioid tubercles typical of Boeck's sarcoid.

FIG. 3. *Case 8.* Before cortisone therapy. Hilar and mediastinal lymph node enlargement is present and there is a fine reticular infiltration throughout both lung fields. Roentgenogram obtained after cortisone therapy was unchanged.

Physiologic studies before treatment showed: an increased total lung capacity and a greatly increased residual volume, with an increased residual volume to total capacity ratio; an increase in the index of intrapulmonary mixing; a reduced maximum breathing capacity; marked hyperventilation; arterial oxygen unsaturation at rest and after exercise; a reduced oxygen diffusing capacity; abnormalities of ventilation-perfusion relationships; pulmonary arterial hypertension.

Three hundred milligrams of cortisone were given by injection on May 15, 1951; 200 mg. per day were given on the next two days, 150 mg. per day for the next five days, 100 mg.

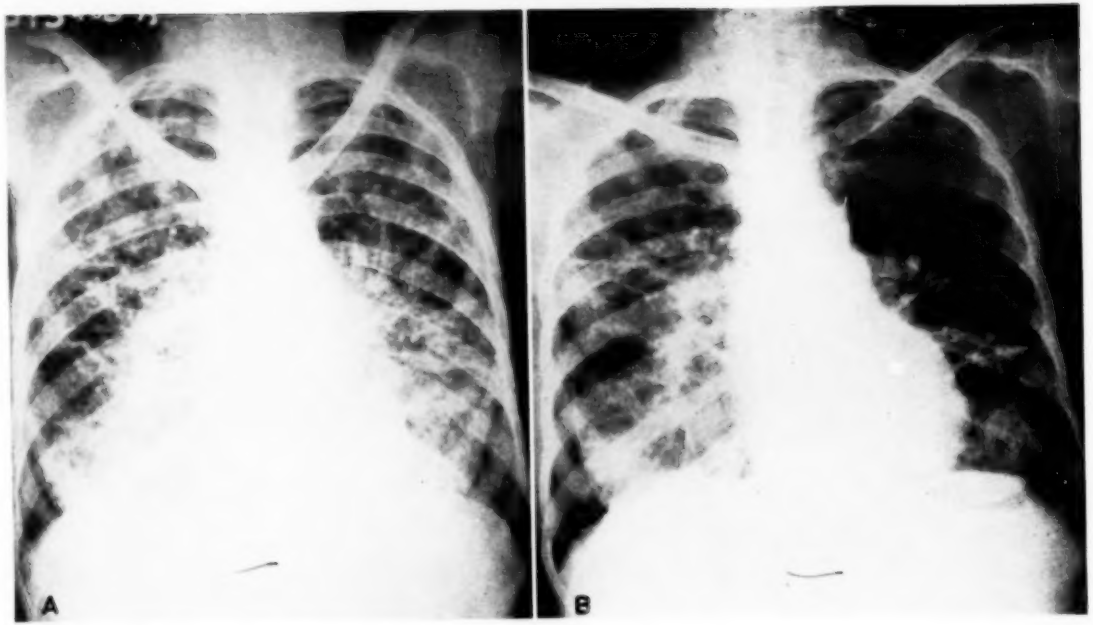


FIG. 4. *Case 10*

A. Before cortisone therapy. In both lung fields there are dense, linear and nodular infiltrations. Emphysematous bullae can be seen at the periphery in both lungs.

B. After cortisone therapy. Marked resolution of the infiltration has occurred. Liver infiltrations are still present and the emphysematous bullae are unchanged.

per day for the next three weeks, and 75 mg. per day for the remainder of the patient's stay in the hospital. During the first week of cortisone therapy, a marked sense of well-being developed and dyspnea decreased. In the first two weeks there was a marked decrease in the size of her spleen and liver. Biopsy of the liver was repeated after one month of cortisone therapy. Only small areas of dense fibrous tissue were seen. A roentgenogram of the chest (figure 4*B*) showed marked, but incomplete, clearing of her pulmonary infiltrations and persistence of the emphysematous bullae.

During this first course of cortisone therapy, physiologic studies (tables 2 through 5) showed an increase in the vital capacity and a decrease in the residual volume and in the residual volume to total capacity ratio. The arterial oxygen saturation and the per cent of venous admixture in the arterial blood returned to normal. The maximum breathing capacity, the oxygen diffusing capacity, and the pulmonary arterial pressures showed no significant change.

After discharge from the hospital, therapy was continued with 50 mg. of cortisone per day by mouth, and symptomatic improvement was maintained. Treatment was continued until September, 1951, when the patient was lost from clinic supervision. She was seen next in January, 1952, complaining of a recurrence of her respiratory symptoms, of blood spitting, and bleeding from her mucous membranes. Her spleen and liver were found to have increased in size, and the presence of thrombocytopenic purpura was established. This condition was successfully controlled by a short course of cortisone. Cortisone was discontinued, and splenectomy was carried out.

In March, 1952, during this relapse, physiologic studies (tables 2 through 5) revealed a marked decrease in the patient's resting arterial oxygen saturation, and a definite increase in the venous admixture was found.

Treatment with cortisone was resumed, with a dosage schedule comparable with that used at the time of her first treatment. Her dyspnea decreased, and she was able to perform light exercise. She was again discharged, to be followed as an outpatient, taking 50 mg. of cortisone by mouth.

During the second course of treatment, the arterial oxygen saturation at rest returned nearly to normal, and the alveolar-arterial gradients decreased at both levels of inspired oxygen. There was no significant change, however, in the measurements of the lung volumes; marked arterial oxygen unsaturation appeared on exercise and the still large alveolar arterial oxygen tension gradients were evidence that oxygen transport remained severely disturbed and pulmonary hypertension had decreased somewhat.

In summary, this patient had lung volume changes and disturbances in gas exchange similar to those seen in severe chronic pulmonary emphysema. With cortisone therapy, there was a satisfactory clinical response, striking roentgenographic clearing of pulmonary infiltrations, and improvement in the oxygen transport to the pulmonary capillaries. This improvement resulted from a decrease in the venous admixture in the arterial blood without any significant change in the oxygen diffusing capacity. Furthermore, the lung volume changes consistent with chronic pulmonary emphysema persisted. From these findings it is apparent that the emphysematous lesions in this case were not reversible by hormonal therapy and played a significant part in the physiologic disturbances.

DISCUSSION

The conflicting results of physiologic studies in pulmonary sarcoidosis so far reported in the literature by different investigators (12, 17–19) are reconciled by the findings in the present study. At least three distinct types of abnormal physiologic pattern have been isolated in this group of 10 patients. It is not unlikely that further studies on a larger group will give better information concerning the relative frequency of each type and their respective inter-relationship in the course of the natural evolution of the disease. The respective roles played by the location, extent, histologic characteristics, and evolution of the lesions in the various physiologic types which have been observed are a subject for speculation. The minimal functional abnormalities observed in the first type might be related to the limited extent of the process and to the lack of involvement of the alveolar-capillary septa and peri-bronchiolar areas. In contrast, the lesions in the second type are probably very extensive and predominantly located in the alveolar capillary septa. They do not differ, therefore, from the granulomatous and fibrous lesions which have been described and discussed as characteristic of the syndrome of alveolar-capillary block (17).

Whether the development of pulmonary emphysema occurs early in some forms of the disease as a result of the predominant peribronchiolar location of the lesion or whether the development of emphysema occurs late has not been ascertained. It is well known that pulmonary emphysema, by a mechanism which is not altogether clear, develops frequently as a late complication of various granulomatous and fibrotic processes in the lung. Whatever the mechanism of development, chronic pulmonary emphysema in Boeck's sarcoid has two distinct features not observed in the common obstructive type of emphysema, i.e., a considerably greater degree of hyperventilation and a lesser disturbance of intrapulmonary gas mixing. Coates and Comroe (18) have found that the index of intrapulmonary mixing in their patients remained normal, and that evidence of poor intrapulmonary gas distribution could only be identified by the very sensitive method developed by Fowler (29). In two of their cases the hyperventilation was greater than in any of the sixty-eight cases of chronic pulmonary emphysema studied by Baldwin and associates (30). This considerable hyperventilation obviously minimized the effect of poor gas distribution upon the index of intrapulmonary mixing.

In the absence of biopsies of the lung before and after cortisone therapy, it is difficult to decide why no uniform response to therapy has been observed in the present series. From the results of the extrapulmonary biopsies, it appears that granulomatous lesions tend to become fibrotic under treatment. Whether a similar process takes place in the lungs is unproved, but it is likely that it does. Therefore, it might be assumed that changes in pulmonary function associated with hormonal therapy are related to the degree of resolution of the granuloma and to the extent of the resulting fibrosis. Thus, failure of improvement in pulmonary function might be due to the development of a severe fibrosis. It might also be due to the fact that before treatment the pulmonary lesions were chiefly fibrotic. These same considerations might also be invoked in order to explain the variable

and, as a rule, insignificant influence of cortisone treatment upon the hemodynamic findings.

The question remains of the value of physiologic studies in the treatment of Boeck's sarcoid. Apparently they are not particularly helpful in the selection of cases which will benefit from hormonal therapy. Perhaps the two greatest values are: first, to confirm clinical impressions concerning the severity of the disease and to demonstrate disturbances in pulmonary gas exchange, which is important since, in the mild form characterized only by a mild degree of ventilatory insufficiency, treatment seems unwarranted at the present time; second, to provide objective measurements of the effect of treatment since they are independent of the patient's interpretation and are not influenced by the sense of well-being which so often accompanies cortisone therapy.

SUMMARY

The previously reported physiologic findings in patients with Boeck's sarcoid with pulmonary involvement and the reported effects of cortisone on the function abnormalities have been reviewed. Ten additional cases of pulmonary sarcoidosis in which cardiopulmonary function studies were performed have been presented; the clinical, physiologic, and pathologic effects of cortisone therapy are reported in 5 of these cases.

Three types of pulmonary functional abnormalities have been observed in pulmonary sarcoidosis. In the first type, the reduction in lung volumes is associated with mild hyperventilation and an inconstant decrease in maximum breathing capacity. In the second type, the reduction in lung volumes is associated with disturbances in alveolar-capillary gas exchanges characteristic of the syndrome of alveolar-capillary block. In the third type, the lung volume changes and disturbances in alveolar-capillary gas exchanges are consistent with chronic pulmonary emphysema.

Of the 5 patients treated with cortisone, 2 with impairment of alveolar-capillary oxygen diffusion and the one with an emphysema-like pattern showed definite physiologic improvement. In all cases in which biopsy material was available, there was a change during therapy in the histologic characteristics of the lesion from a granulomatous to a more fibrotic process.

The different patterns of pulmonary dysfunction and the variable effects of cortisone therapy are presumably related to the location, extent, histologic characteristics, and evolution of the pulmonary lesions. Proof of these relationships in terms of pathologic changes, however, is still lacking.

SUMARIO

La Función Cardiopulmonar en la Forma Pulmonar del Sarcoides de Boeck y su Modificación por la Cortisonoterapia

Repásanse aquí los hallazgos fisiológicos previamente comunicados en enfermos con el sarcoides de Boeck y difusión pulmonar y los efectos de la cortisona sobre las anomalías funcionales que se han descrito. Preséntanse otros 10 casos de sarcoidosis pulmonar en que

se ejecutaron estudios de la función cardiopulmonar, con los efectos clínicos, fisiológicos y patológicos de la cortisonoterapia en 5 de ellos.

En la sarcoidosis pulmonar, observáronse tres formas de anomalías de la función pulmonar. En la primera, la reducción del volumen pulmonar va unida a ligera hiperventilación e inconstante disminución de la capacidad respiratoria máxima. En la segunda, la reducción de los volúmenes pulmonares se asocia a trastornos de los intercambios alvéolo-capilares de gases, que son típicos del síndrome de bloqueo alvéolo-capilar. En la tercera, las alteraciones del volumen pulmonar y los trastornos de los intercambios alvéolo-capilares de gases son compatibles con la presencia de enfisema pulmonar crónico.

De los 5 enfermos tratados con cortisona, 2 con insuficiente difusión alvéolo-capilar de oxígeno y el único que mostraba un patrón enfisematoideo, revelaron mejoría fisiológica bien definida. En todos los casos en que había disponibles ejemplares biópsicos, se modificaron, durante la terapéutica, las características histológicas de la lesión: de proceso granulomatoso a más fibroso.

Los diversos patrones de la disfunción pulmonar y los distintos efectos de la cortisonoterapia se relacionan presuntamente con la localización, difusión, características histológicas y evolución de las lesiones pulmonares. Sin embargo, todavía falta la prueba patológica de esas relaciones.

RESUME

Fonction cardio-pulmonaire dans la forme pulmonaire de la sarcoïdose de Boeck et sa modification par la cortisonothérapie

Les résultats physiologiques précédemment rapportés chez des malades atteints de sarcoïdose de Boeck avec lésions pulmonaires et les effets de la cortisonothérapie sur les anomalies fonctionnelles sont passés en revue. Dix cas additionnels de sarcoïdose pulmonaire, dans lesquels l'étude de la fonction cardio pulmonaire a été faite, sont présentés; les auteurs exposent les effets cliniques, physiologiques et pathologiques de la thérapie par la cortisone observés dans cinq de ces cas.

Trois types d'anomalies fonctionnelles ont été observés dans la sarcoïdose pulmonaire. Dans le premier type, la diminution de volume du poumon s'associe à une hyperventilation modérée et une réduction inconstante de la capacité de ventilation maxima. Dans le deuxième type, la réduction de volume du poumon s'associe à des altérations des échanges gazeux, caractéristiques du syndrome de blocage alvéolo-capillaire. Dans le troisième type, les modifications du volume du poumon et l'altération des échanges gazeux sont caractéristiques de l'emphysème pulmonaire chronique.

Dans un groupe de 5 malades traités par la cortisone, l'amélioration s'est manifestée par des signes physiologique indubitables chez 2 malades présentant une altération de la diffusion alvéolo-capillaire de l'oxygène et chez un malade emphysémateux. Dans tous les cas où l'examen biopsique a été possible, on a pu observer, au cours de la thérapie, une modification des caractères histologiques de la lésion; le processus granulomateux a évolué vers la sclérose.

Les différents aspects de la dysfonction pulmonaire et les effets variables de la cortisonothérapie sont probablement en rapport avec le siège, l'étendue, les caractères histologiques et l'évolution des lésions pulmonaires. Toutefois la preuve pathologique de leurs relations mutuelles n'est pas encore faite.

REFERENCES

(1) Pinner, M.: Noncaseating tuberculosis, Am. Rev. Tuberc., 1938, *37*, 690.

(2) Longcope, W. T.: Sarcoidosis or Besnier-Boeck-Schaumann disease, J. A. M. A., 1941, *117*, 1321.

(3) Ricker, W., and Clark, M.: Sarcoidosis, a clinico-pathological review of twenty-two autopsies, Am. J. Clin. Path., 1949, *19*, 725.

(4) Reisner, D.: Boeck's sarcoid and systemic sarcoidosis, Am. Rev. Tubere., 1944, *49*, 289 and 437.
(5) Freiman, D. G.: Medical progress: Sarcoidosis, New England J. Med., 1948, *239*, 664, 709, and 743.
(6) Mallory, T. B.: Pathology of pulmonary fibrosis, including chronic pulmonary sarcoidosis, Radiology, 1948, *51*, 468.
(7) Longcope, W. T., and Freiman, D. G.: A study of sarcoidosis, Medicine, 1952, *31*, 1.
(8) Bruce, T., and Wassen, E.: Clinical observations on the course and prognosis of lymphogranulomatosis benigna Schaumann, particularly in regard to pulmonary lesions, Acta med. Scandinav., 1940, *104*, 63.
(9) Dressler, M.: Ueber die Lungenbeteiligung bei der Granulomatosis benigna, Ergebn. d. inneren Medizin u. Kinderheilkunde, 1942, *62*, 282.
(10) Leitner, S. J.: Elektrokardiographische und spirometrische Untersuchungen bei der Epitheliodzelligen Granulomatose (Morbus Besnier Boeck Schaumann), Cardiologia, 1946, *10*, 379.
(11) Leitner, S. J.: Der Morbus Besnier-Boeck-Schaumann, Benno Schwabe, Basel, 1949.
(12) Baldwin, E. deF., Cournand, A., and Richards, D. W., Jr.: Pulmonary insufficiency: II. A study of thirty nine cases of pulmonary fibrosis, Medicine, 1949, *28*, 1.
(13) Galdston, M., Weisenfeld, S., Benjamin, B., and Rosenbluth, M. D.: Effect of ACTH in chronic lung disease, Am. J. Med., 1951, *10*, 166.
(14) Wright, G. W., and Filley, G. F.: Pulmonary fibrosis and respiratory function, Am. J. Med., 1951, *10*, 642.
(15) Riley, R. L., and Cournand, A.: Analysis of factors affecting the concentration of oxygen and carbon dioxide in the gas and blood of the lungs: I. Theory, J. Appl. Physiol., 1951, *3*, 77.
(16) Riley, R. L., Donald, K. W., and Cournand, A.: Analysis of factors affecting the concentration of oxygen and carbon dioxide in the gas and blood of the lungs: II. Methods, J. Appl. Physiol., 1951, *3*, 102.
(17) Austrian, R., McClement, J. H., Renzetti, A. D., Jr., Riley, R. L., Donald, K. W., and Cournand, A.: The clinical and physiological features of some types of pulmonary diseases with impairment of alveolar capillary diffusion, Am. J. Med., 1951, *11*, 667.
(18) Coates, E. O., and Comroe, J. H., Jr.: Pulmonary function studies in sarcoidosis, J. Clin. Investigation, 1951, *30*, 848.
(19) Lukas, D. K.: Some effects of adrenocorticotropic hormone and cortisone on pulmonary function of patients with obstructive emphysema, Am. Rev. Tubere., 1951, *64*, 279.
(20) Sanes, M., Israel, H. L., Dratman, M. B., and Frank, J. H.: Effect of cortisone in sarcoidosis, New England J. Med., 1951, *244*, 200.
(21) Siltzbach, L. E., Posner, A., and Medline, M. M.: Cortisone therapy in sarcoidosis, J. A. M. A., 1951, *147*, 927.
(22) Lovelock, J. J., and Stone, D. J.: Cortisone therapy of Boeck's sarcoid, J. A. M. A., 1951, *147*, 930.
(23) Small, M. J.: Favorable response of sarcoidosis to cortisone treatment, J. A. M. A., 1951, *147*, 932.
(24) Siltzbach, L. E.: Effects of cortisone in sarcoidosis, Am. J. Med., 1952, *12*, 139.
(25) Baldwin, E. deF., Cournand, A., and Richards, D. W., Jr.: Pulmonary insufficiency: I. Physiological classification, clinical methods of analysis, standard values in normal subjects, Medicine, 1948, *27*, 243.
(26) Riley, R. L., Proemmel, D. D., and Franke, R. E.: A direct method for determination of oxygen and carbon dioxide tensions in blood, J. Biol. Chem., 1945, *161*, 621.

(27) Cournand, A., Baldwin, J. S., and Himmelstein, A.: Cardiac catheterization in congenital heart disease, The Commonwealth Fund, New York, 1949, ch. I, p. 6.

(28) McClement, J. H., Renzetti, A. D., Jr., Carroll, D., Himmelstein, A., and Cournand, A.: Cardiopulmonary function in hematogenous pulmonary tuberculosis in patients receiving streptomycin therapy, Am. Rev. Tubere., 1951, *64*, 583.

(29) Fowler, W. S.: Lung function studies: III. Uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease, J. Appl. Physiol., 1949, *2*, 283.

(30) Baldwin, E. deF., Cournand, A., and Richards, D. W., Jr.: Pulmonary insufficiency: III. A study of 122 cases of chronic pulmonary emphysema, Medicine 1949, *28*, 201.

THE EFFECT OF STREPTOMYCIN THERAPY ON THE BRONCHOCAVITARY JUNCTION AND ITS RELATION TO CAVITY HEALING[1,2]

OSCAR AUERBACH,[3] HARRY L. KATZ, AND MAURICE J. SMALL[3]

(Received for publication August 26, 1952)

INTRODUCTION

Although streptomycin therapy has been in use for the past six years in the treatment of chronic pulmonary tuberculosis, there are still many problems in regard to this therapeutic agent which remain unanswered and require further study. Prominent among these are the most efficient dosage schedule, the ideal duration of therapy, and the fate of the tubercle bacilli in the cavities which close under this form of therapy.

Since the addition of para-aminosalicylic acid (PAS) to streptomycin therapy, treatment schedules have been greatly prolonged. During this period of prolonged therapy, great decrease in the size of cavities and, in many instances, the complete loss of cavities from view on serial roentgenograms have frequently been observed.

Anatomic studies on the effect of streptomycin on chronic pulmonary tuberculosis have been few in number (1–7) and do not include mention of any specific streptomycin effect on the bronchocavitary junction. It is probable that this may be due chiefly to the fact that most of the observations were made on autopsy material in which, in most instances, the infecting organisms had become resistant to the drug. Another factor may be that many of the anatomic studies were made before the addition of PAS to treatment regimens and thus are short-term therapy cases. Mahon (4) does mention, however, the lack of active endobronchial disease adjacent to smaller cavities.

In a study of excised specimens from patients who have been treated with streptomycin, the present writers have been impressed with the fact that "closure" of cavities, in many instances at least, is a process entirely different from that which occurs in patients not treated with streptomycin. At this time no statistical evaluation can be made since a much longer study will be required; yet the findings are so frequent and consistent that it is believed that a review of the material is justified.

[1] From the Laboratory and Medical Services of the Veterans Administration Hospitals, Staten Island and Brooklyn, New York.

[2] This paper was presented, in part, at the Eleventh Streptomycin Conference of the Veterans Administration at St. Louis, Missouri, January 18, 1952, and before the *Medical Session on Tuberculosis* at the 48th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, on May 27, 1952.

[3] Present address: Veterans Administration Hospital, East Orange, New Jersey.

OBSERVATIONS

Case Reports

Case 1: A 33-year old white male was admitted to Brooklyn Veterans Administration Hospital on October 16, 1950. The onset of symptoms occurred two months prior to admission and consisted of fever, easy fatigability, cough, and right chest pain. Physical examination revealed a temperature elevation to 101°F. Bronchovesicular breath sounds and rales were audible throughout the right upper lobe. The hemogram was normal and the erythrocyte sedimentation rate was 19 mm. per hour. The sputum was positive for *M. tuberculosis* and the bacilli were susceptible to a concentration of 1γ of streptomycin per ml. The admission chest roentgenogram (figure 1*A*) revealed a fibro-exudative infiltration in the right upper lobe, multiple cavities within this lobe, and scattered soft infiltrations in the right lower lobe.

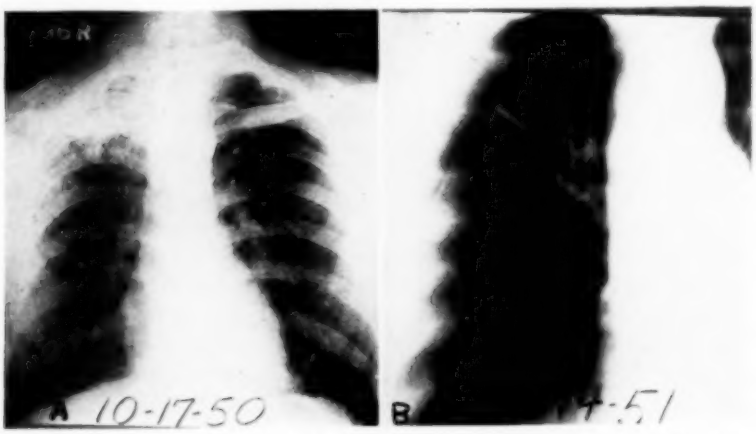


FIG. 1*A*. October 17, 1950. Admission roentgenogram. Fibro-exudative infiltration and multiple small cavities in right upper lobe. Scattered soft infiltrations are also present in the lower lobe.

FIG. 1*B*. March 14, 1951. Tomogram. Residual cavities in the right upper lobe are distinctly seen.

In addition to bed rest, streptomycin, 1 gm. daily, and PAS, 12 gm. daily, were started October 26, 1950. This therapy was continued until February 22, 1951, at which time the streptomycin dosage was changed to 1 gm. twice weekly and continued until July 23, 1951, to a total dosage of 170 gm. Right pneumothorax was induced on December 22, 1950, but was abandoned as ineffectual because of pleural adhesions. Bronchoscopic examination on March 27, 1951, revealed a normal tracheobronchial tree.

Serial chest roentgenographic examinations including tomography (figure 1*B*) revealed moderate resolution of the infiltrations in the right upper lobe. Nevertheless, residual multiple small cavities remained. Cultures of sputum and gastric contents remained persistently negative for *M. tuberculosis* after January, 1951.

Resection of the right upper lobe and a wedge resection of the apical segment of the right lower lobe were performed on April 4, 1951. The total dosage of streptomycin which had been administered at the time of resection was 130 gm. Smears from the resected specimen were negative, but the cultures were positive for *M. tuberculosis* and the bacilli were sus-

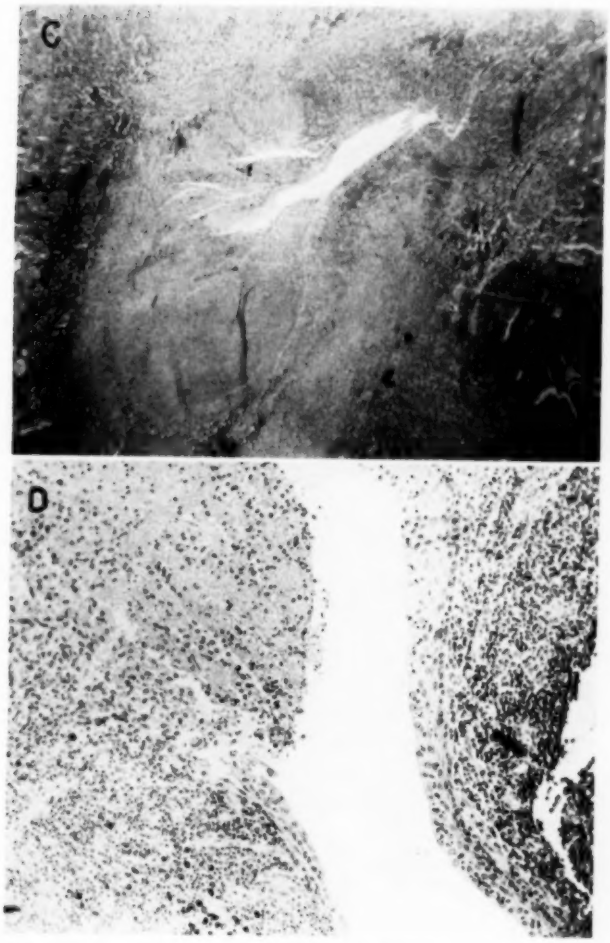


FIG. 1C. Low power view of one of the inspissated (filled in) cavities in the right upper lobe. The lumen of the cavity is almost completely filled with necrotic material. A patent bronchus leads into the cavity.

FIG. 1D. A high power view of figure 1C at the bronchocavitary junction. The bronchus is lined by a layer of squamous epithelium which extends along the cavity wall for a short distance. Neutrophils are present in the epithelial layer. The epithelium stops at the point where the cavity wall is lined by necrotic material.

ceptible to 1γ of streptomycin per ml. A "tailoring" thoracoplasty was performed in June, 1951, and the postoperative course was uneventful. Sputum, gastric contents, and tracheal washings remained persistently negative for *M. tuberculosis* on concentration and culture. The patient was discharged from active hospital care on October 24, 1951.

Pathologic findings: The specimen of the right upper lobe measured 17 by 9 by 4 cm. Present in the upper 5 cm. of the lobe, chiefly in the posterior and lateral aspects, were a large number of foci. Some of these were gray and firm and measured from less than 1 to 1 ml. in diameter, and many were contiguously arranged. Other larger foci were yellow and inspissated. Bronchi could be traced into the cavity lumen.

Microscopic examination revealed that some of the yellow foci represented "filled in" cavities, and in one of these a branch of the right upper lobe bronchus communicated with the cavity. At the bronchocavitary junction the columnar epithelium of the bronchus gave way to squamous epithelium (figures *1C* and *1D*). The epithelium extended for some distance along the inner wall of the cavity.

Case 2: A 48-year-old white male was admitted to Brooklyn Veterans Administration Hospital on September 1, 1950, with a history of the onset of symptoms in July, 1950, with cough, weight loss of approximately twenty pounds, weakness, fatigability, and right chest pain.

Examination of the chest revealed a lag of the right hemithorax on deep inspiration, dullness to percussion, and bronchial breath sounds in the region of the right upper lobe. Moist rales were audible throughout the upper half of the right chest.

Hemogram, routine urinalyses, and serologic tests for syphilis yielded normal findings. The erythrocyte sedimentation rate was 22 mm. per hour. The sputum was positive for tubercle bacilli (Gaffky IX) which were susceptible to 1γ of streptomycin per ml. The chest roentgenogram on admission to the hospital revealed an extensive caseopneumonic process, with multiple large cavities involving the entire right upper lobe. A bronchogenic seeding was present in the right lower lobe, left mid-lung field, and base. The trachea was deviated to the right.

In addition to bed rest, streptomycin, 1 gm. daily, and PAS, 12 gm. daily, were started on September 15, 1950, and continued to January 13, 1951, when the streptomycin regimen was changed to 1 gm. twice weekly.

Serial chest roentgenograms (figure 2A) revealed progressive resolution, contraction of the disease in the right upper lobe, and progressive stabilization of the disease in the left lung. Tomographic examination revealed multiple residual areas of tissue breakdown within the contracted right upper lobe.

Bronchoscopic examination on November 2, 1950, showed multiple small areas of ulceration in the right main bronchus. The mucosa was markedly edematous and inflamed. Repeat bronchoscopy on March 16, 1951, revealed complete healing of the ulcerations and subsidence of the inflammatory reaction in the right main bronchus.

After November, 1950, all sputum and gastric content examinations were negative for tubercle bacilli on concentration and culture with the exception of two sputum specimens which showed a Gaffky I in January, 1951.

On April 25, 1951, a right upper lobe lobectomy was performed. At this time the total amount of streptomycin which had been administered was 150 gm. A "tailoring" thoracoplasty with the removal of segments of the second, third, fourth, and fifth ribs was performed June 8, 1951. Bacteriologic studies showed the resected specimen to be negative for tubercle bacilli on smear and culture.

The postoperative course was uneventful. Streptomycin, 1 gm. twice weekly, and PAS were continued until August 6, 1951, to a total dosage of 180 gm.

The sputum, gastric contents, and tracheal exudate remained persistently negative for tubercle bacilli on concentration and culture. The patient was discharged from active hospital care on October 26, 1951.

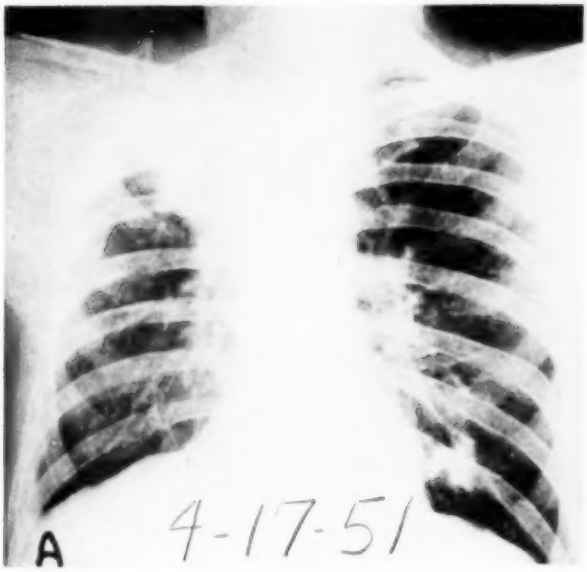


FIG. 2A. April 17, 1951. Preoperative roentgenogram showing considerable clearing of the disease bilaterally and retraction of the right upper lobe.

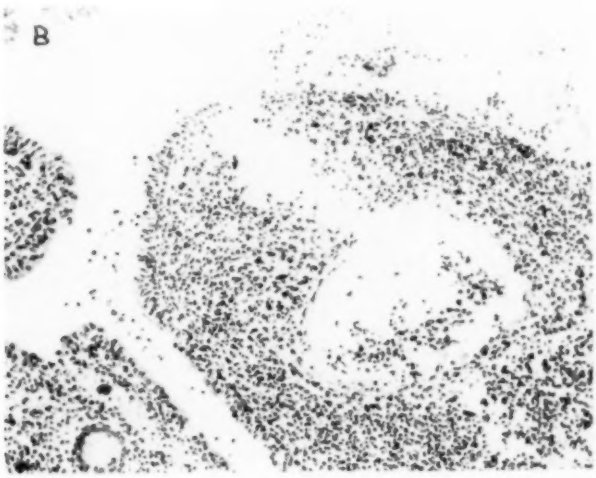


FIG. 2B. Photomicrograph of a bronchus at the bronchocavitary junction showing a columnar epithelial lining over a portion of the wall which has been extensively altered by the tuberculous process; a portion of the cartilage is destroyed. The bronchus leading to the cavity is patent.

Pathologic findings: The resected right upper lobe measured 8 cm. in the apico-basal direction, 7 cm. in the mediolateral direction, and 8 cm. in the antero-medial direction. Irregular gray bands of connective tissue traversed the lung parenchyma. Scattered among these bands were oval and round necrotic foci which varied in size from 0.8 to 1.5 cm.; some of these showed inspissated contents (former cavities). Branches of the upper lobe bronchi could be traced into some of these inspissated foci.

Microscopic examination revealed that much of the lung parenchyma was replaced by dense connective tissue. Lying among these were zones of necrosis which showed the ghost forms of lung parenchyma surrounded by tuberculous granulation tissue. Inspissated cavities with patent communicating bronchi were also present. The epithelium at the bronchocavitary junction was intact and columnar in character (figure 2*B*). In one aspect the intact epithelium covered a portion of cartilage which had been partially destroyed by the tuberculous process.

Case 3: A 49-year-old white male was admitted to Brooklyn Veterans Administration Hospital on July 26, 1951. In 1941, while a prisoner of war, he had recurrent attacks of pleurisy on the right side, diphtheria, malaria, and dysentery. In May, 1951, he had a recurrence of the right chest pain in addition to cough of increasing severity, easy fatigability, night sweats, and progressive weight loss.

He was hospitalized at another institution from May 21, 1951, to June 6, 1951. At that time a chest roentgenogram (figure 3*A*) showed a well-defined cavity in the right upper lobe. The sputum was positive for acid fast bacilli on smear.

Physical examination revealed a well-developed and well-nourished male. His temperature was normal; rales were audible in the region of the right upper lobe posteriorly.

In addition to bed rest, streptomycin, 1 gm. daily, and PAS, 12 gm. daily, were started on August 2, 1951. Pneumoperitoneum was induced on September 26, 1951, and maintained by weekly refills varying from 700 to 1,200 cc. of air.

Serial chest roentgenograms (figure 3*B*) revealed progressive resolution of the exudative infiltration in the right upper lobe. Nevertheless, the cavity, though considerably decreased in size, remained patent. In addition, right lateral tomography revealed a small cavity in the apical segment of the right lower lobe (figure 3*C*).

Sputum and gastric contents remained persistently negative for tubercle bacilli on culture after October, 1951. Susceptibility studies on the last positive gastric culture, September 25, 1951, revealed the bacilli to be resistant to 1 γ and partially susceptible to 5 γ of streptomycin per ml.

On December 5, 1951, right upper lobectomy and segmental resection of the apical segment of the right lower lobe were performed. At this time, 130 gm. of streptomycin had been administered. Bacteriologic studies showed the resected tissue to be negative for tubercle bacilli on smear but positive on culture. The postoperative course was uneventful. Sputum and gastric content cultures remained persistently negative for tubercle bacilli. The patient was discharged from active hospital care on June 15, 1952.

Pathologic findings: The right upper lobe was contracted; the pleura covering it was thickened and smooth. The lobe cut with increased resistance. Many yellowish, encapsulated foci were present. A well-demarcated cavity, which measured 8 mm. in the apico-basal direction, 5 mm. in the mediolateral direction, and 5 mm. in the anteroposterior direction, was present in the posterior segment. This cavity was in direct communication with a bronchus, the cavity

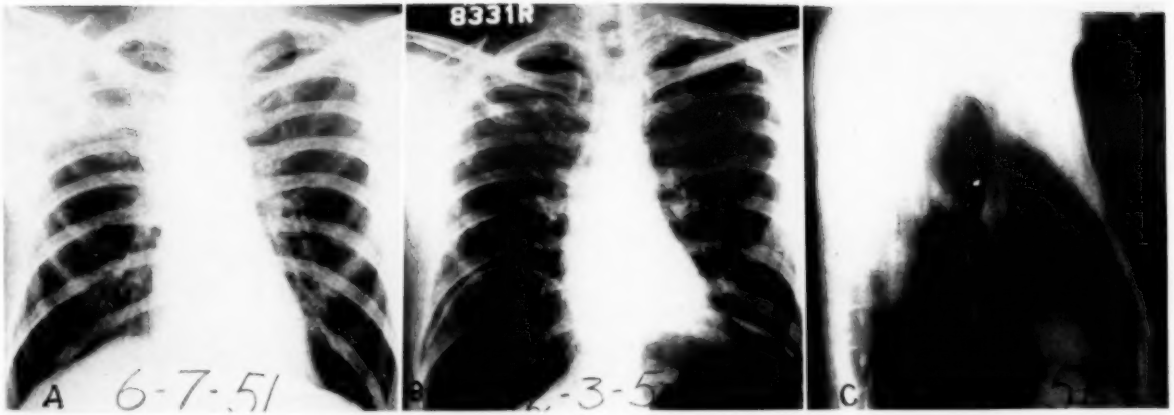


FIG. 3A. June 7, 1951. Initial roentgenogram. Caseous disease is present in the right upper lobe. A cavity is seen in the region of the second anterior rib.

FIG. 3B. August 3, 1951. Considerable resolution of the exudative infiltration in the right upper lobe. The cavity is smaller but still patent. Pneumoperitoneum is present.

FIG. 3C. October 11, 1951. Right lateral tomogram. Cavitation is present in the posterior segment of the right upper lobe and in the superior segment of the right lower lobe.

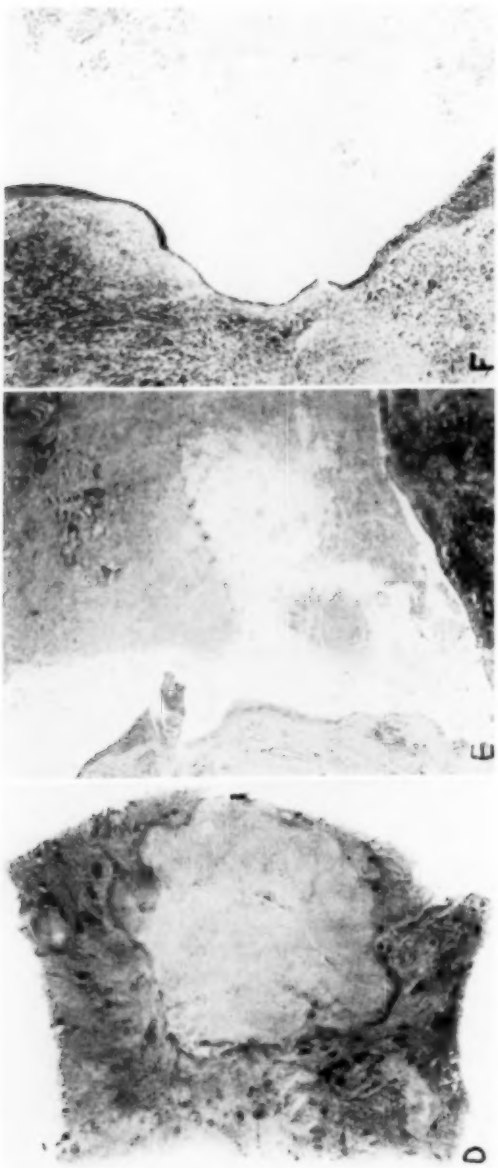


FIG. 3*D*. Photomicrograph of the cavity from the right upper lobe shows the lumen to be filled with necrotic material.

FIG. 3*E*. A higher magnification of 3*D* at the bronchocavitary junction. The columnar epithelium lining the bronchus changes to a flattened and squamous type as it continues along the inner wall of the cavity for some distance. Inspissated necrotic material lies loose in the cavity.

FIG. 3*F*. Photomicrograph of the epithelium lining the cavity shows it to lie on a zone of granulation tissue; it is squamous in some regions and flattened in others.

wall was lined by a grayish membrane, and the lumen was partially filled with necrotic material.

In the superior segment of the right lower lobe, two cavities, which measured 1 cm. and 7 mm. in diameter, respectively, were present. Several small encapsulated foci were scattered through this segment.

Microscopic examination of the cavity and the draining bronchus from the right upper lobe showed a wide communication between the cavity and the bronchus (figures 3*D* and *E*). The lumen of the cavity was partially filled with necrotic material surrounded by granulation tissue which contained an abundance of collagen fibrils. The epithelial lining of the bronchus was columnar in character. At the bronchocavitary junction there was a transition to both flattened and squamous types. The epithelium continued around the inner wall for some distance on either side (figure 3*F*). Beyond the epithelial lining was granulation tissue continuous with that surrounding the necrotic zone which formed the inner lining of the cavity in the more distal aspects.

Case 4: A 23 year old white male was admitted to Halloran Veterans Administration Hospital on November 7, 1949. The history suggested that the onset of symptoms had occurred approximately three months prior to admission, with a sensation of chilliness, an intermittent feverish feeling, cough productive of four to six ounces of yellowish green sputum, easy fatigability, and night sweats. The admission diagnosis was putrid lung abscess involving the apical segment of the right lower lobe.

Physical examination revealed increased vocal and whispered fremitus in the region of the right mid lung field and numerous coarse, moist rales in this area. Hemogram, urine findings, and serologic tests for syphilis were normal. The sputum was positive for tubercle bacilli (Gaffky V) and the bacilli were susceptible to 1 γ of streptomycin per ml. Chest roentgenogram on admission (figure 4*A*) revealed a large cavity in the apical segment of the right lower lobe.

In addition to bed rest, streptomycin, 1 gm. daily, and PAS, 12 gm. daily, were started November 17, 1949. Bronchoscopic examination on December 20, 1949, revealed a normal tracheobronchial tree. Streptomycin-PAS therapy was continued for ninety days until February 14, 1950, at which time the bacilli were still susceptible to 1 γ of streptomycin per ml.

Serial chest roentgenograms revealed progressive diminution in size of the cavity. In January, 1950, a small and well-defined cavity was visualized only on right lateral tomography.

On March 21, 1950, right lower lobectomy was performed. The postoperative course was uneventful. Postoperatively, all examinations of sputum and gastric contents were negative for tubercle bacilli on culture.

Pathologic findings: The resected right lower lobe measured 14 cm. apicobasally, 9.5 cm. mediolaterally, and 5 cm. anteroposteriorly. In the lateral portion of the lobe and 1 cm. from the superior border was a cavity, 1 cm. in diameter, lined by a necrotic zone. A branch of the right lower lobe bronchus opened into this cavity. Scattered throughout the lobe were many acinous foci and an occasional necrotic focus surrounded by a well-defined gray capsule.

Microscopic examination revealed that the cavity was lined in most regions by a necrotic zone. At the bronchocavitary junction on one surface was a layer of squamous epithelium which was continuous with the necrotic lining. A zone

of granulation tissue was present beyond the necrotic zone and the layer of squamous epithelium. In the lumen of the cavity there was a focus of granulation tissue which contained an abundance of collagen fibrils (figures 4*B* and *C*).

Case 5: A 30-year-old white male was admitted to Halloran Veterans Administration Hospital on January 19, 1950, because of recurrent hemoptyses and cough of increasing severity.

In November, 1944, a pulmonary lesion was found on routine chest roentgenography. The patient was promptly hospitalized, and a chest roentgenogram revealed an infiltration

FIG. 4A. November 15, 1949. Tomogram. A large cavity occupies the superior segment of the right lower lobe.

with cavity formation in the left upper lobe. The sputum was positive for acid-fast bacilli. In January, 1945, a left pneumothorax was induced which was maintained for the next five years. The sputum promptly became negative for acid-fast bacilli although the collapse was contraselective in type.

On admission to Halloran Veterans Administration Hospital, a chest roentgenogram revealed hydropneumothorax on the left side, considerable pleural thickening, and a cavity in the left upper lobe. The sputum was positive for acid-fast bacilli on smear. Pneumoperitoneum was induced on January 22, 1950. Streptomycin, 1 gm. daily, and PAS, 12 gm. daily, were started on January 27, 1950, and continued until May 26, 1950, for a total of 120 gm. of streptomycin.

Left thoracoplasty and decortication were contemplated but were deferred because of sudden onset of left chest pain, dyspnea, temperature elevation, and roentgenographic evidence of the accumulation of fluid in the right pleural space. Aspiration of the pneumo-

peritoneum resulted in prompt subsidence of all symptoms and the pleural fluid was resorbed within three weeks.

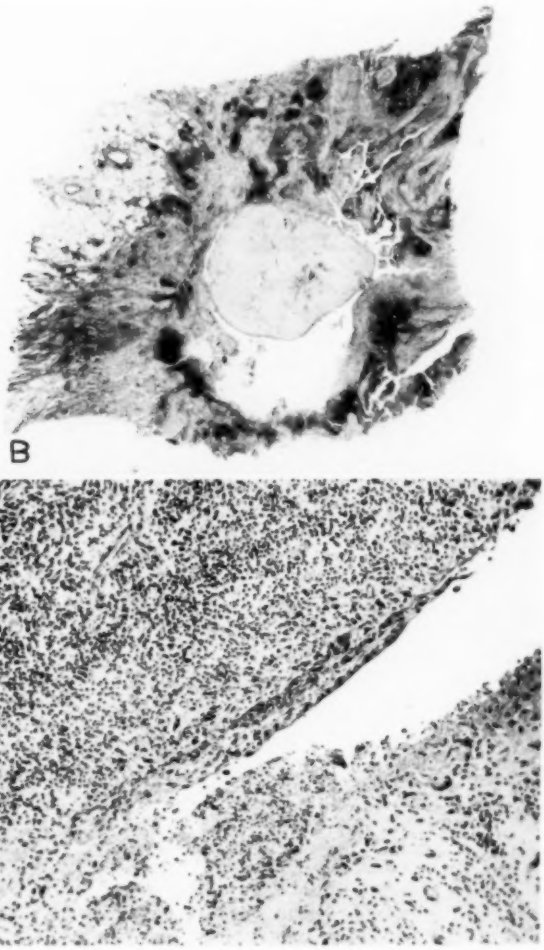


FIG. 4B. Photomicrograph of cavity from the right lower lobe showing much of the lumen to be occupied by a mass of granulation tissue and small necrotic fragments.

FIG. 4C. A high power view of 4B at the bronchocavitary junction showing one surface to be lined by a thick layer of squamous epithelium lying on a zone of granulation tissue; the opposite surface is lined by a necrotic zone which is surrounded by a wide layer of tuberculous granulation tissue.

In August, 1950, it was noted that the patient had roentgenographic evidence of progression of the disease in the left upper lobe (figure 5A). Culture of the sputum at this time was positive for tubercle bacilli, the first positive culture since admission seven months pre-

viously, and the bacilli were still susceptible to 1 γ of streptomycin per ml. Streptomycin and PAS in the same dosage as previously were again given until November 26, 1950, for a total dosage of 90 gm. of streptomycin. The patient thus received a grand total of 210 gm. of streptomycin in the two courses.

On October 19, 1950, segmental resection of the apical posterior segment of the left upper lobe and decortication of the remaining lung were performed. This was followed by a two stage "tailoring" thoracoplasty.

The postoperative course was uneventful; repeated sputum and gastric content cultures were negative for tubercle bacilli.

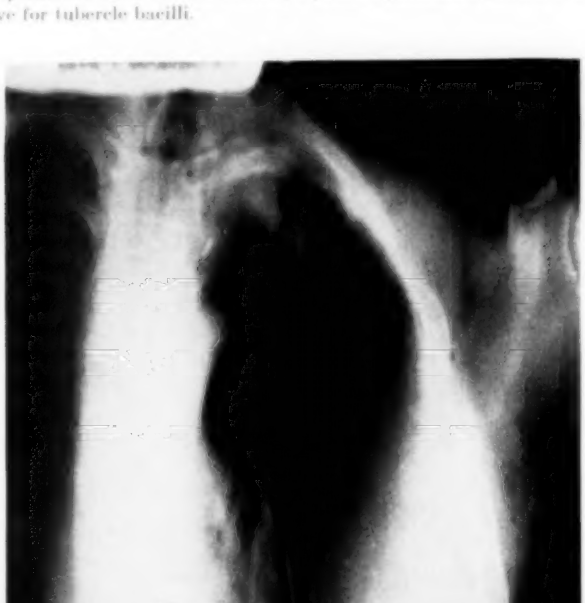


FIG. 5A. August 18, 1950. Tomogram showing small areas of rarefaction in the left upper lobe.

Pathologic findings: The resected segment measured 8 cm. apico-basally, 4.5 cm. mediolaterally, and 3 cm. anteroposteriorly. A 6 mm. inspissated cavity was present 3 mm. below the apical pleura. The wall of this cavity measured from 2 to 3 mm. in thickness. The apical-posterior bronchus communicated with the cavity, the lumen of which was filled with gelatinous mucoid material. Large portions of pleura were also present, the largest measuring 10 by 21 cm. These were of cartilagenous consistency and varied from 1 to 4 mm. in thickness.

Microscopic examination revealed that the lumen of the inspissated cavity was filled with dense necrotic material in which most of the underlying lung

structure had disappeared (figure *5B*). Large irregular calcium deposits were present within the center of the necrotic mass. In most regions a narrow space intervened between the necrotic mass and the cavity wall. The cavity wall was lined

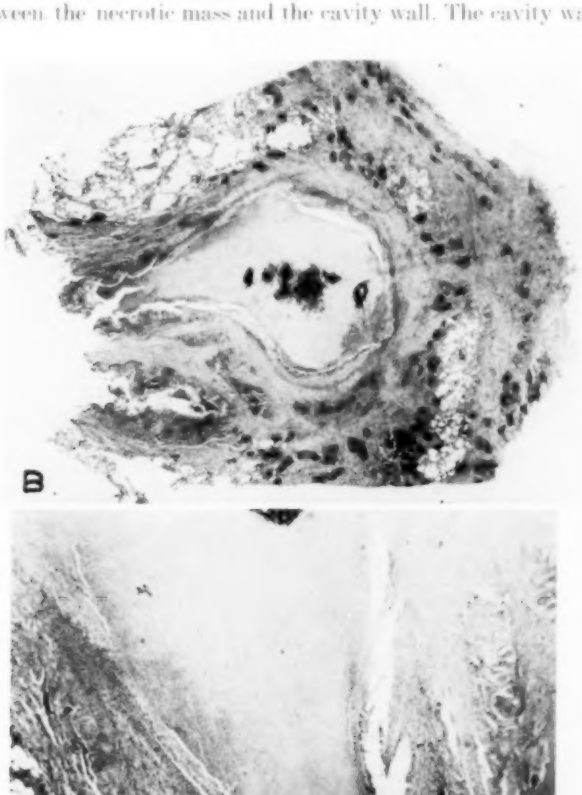


FIG. *5B*. Photomicrograph of the inspissated cavity with a widely patent draining bronchus lined by intact ciliated columnar epithelium. The inspissated necrotic material fills the lumen of the cavity and extends into the lumen of the bronchus for a short distance. Irregular calcium deposits are present within the necrotic mass.

FIG. *5C*. Higher power of figure *5B* at bronchocavitary junction showing abrupt interruption of the columnar epithelium where the bronchus joins the cavity.

by a narrow zone of necrosis, and a wide zone of granulation tissue surrounded the necrotic lining. The bronchus opened widely into the cavity and was lined by intact ciliated columnar epithelium which was interrupted abruptly at its

junction with the cavity by the necrotic layer lining the inner wall of the cavity (figure 5C). The necrotic mass filling the cavity protruded into the bronchial lumen for some distance.

Case 6: In June, 1947, a 41-year-old white male was discovered to have pulmonary tuberculosis with cavitation in the right upper lobe. A right pneumothorax was unsuccessfully attempted, and a thoracoplasty was planned but deferred because of spread of disease to the right lower lobe.

The patient was admitted to Halloran Veterans Administration Hospital in July, 1948. A chest roentgenogram showed cavitary disease involving all lobes of the right lung and scattered infiltrations throughout the left lung (figure 6A). The patient was treated with

FIG. 6A. July 8, 1948. Admission roentgenogram, showing extensive disease with cavitation involving all lobes of the right lung; scattered infiltrations in the left lung.

FIG. 6B. November 8, 1949. Right lateral tomogram, showing localization of multiple large cavities in the right upper lobe and apical segment of right lower lobe.

streptomycin, 0.5 gm. twice a day, for forty-two days. Response to therapy was good, and by December, 1948, a right pneumonectomy was planned. However, the patient left the hospital against medical advice.

He was readmitted to the hospital in October, 1949. In the interim he had received pneumoperitoneum at another institution and his condition was essentially unchanged. At the time of his second admission, the right lung was extensively excavated (6*B*) and the sputum contained many tubercle bacilli. Pneumoperitoneum had been abandoned shortly prior to this admission. Streptomycin, 1 gm. daily, and PAS, 12 gm. daily, were begun in January, 1950, in preparation for right pneumonectomy. The operation was performed on March 3, 1950, after a total of 86 gm. of streptomycin had been given. A seven rib "tailoring" thoracoplasty was done April 10, 1950.

For several months postoperatively the sputum remained positive for tubercle bacilli. The source for this was not discovered until left lateral tomograms taken in August, 1950, revealed a 1 cm. cavity in the lingula of the left lung. When conventional films were then carefully re-examined, it became apparent that this cavity had actually been present at the time of pneumonectomy but had not been recognized because of its small size and position underlying a rib.

Streptomycin PAS therapy was again begun, and pneumoperitoneum was reinstituted. By October, 1950, the small cavity in the left lung had become inspissated and the sputum had become negative for tubercle bacilli; streptomycin was discontinued shortly thereafter. Repeated smears and cultures of sputum and gastric contents were negative for tubercle

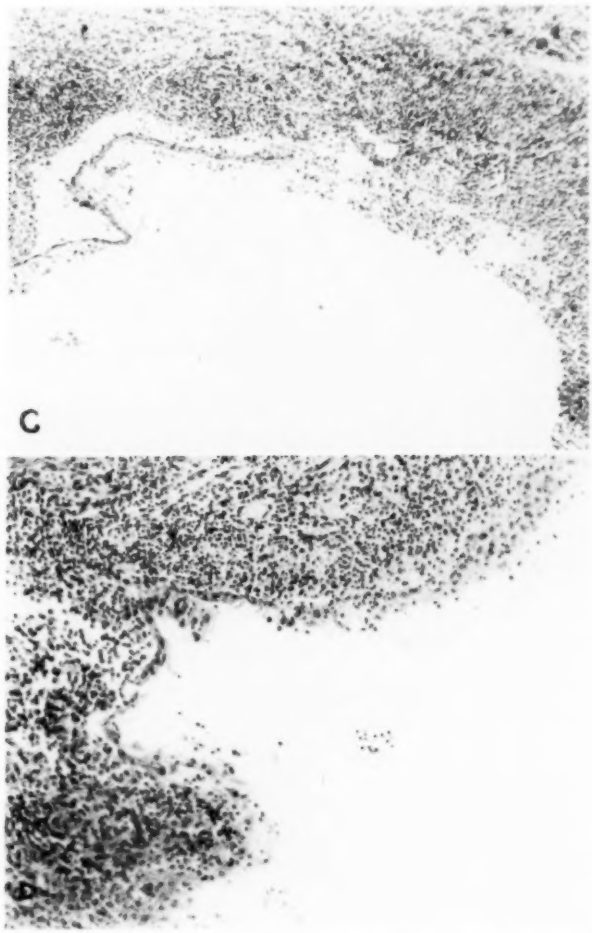


FIG. 6C. High power view of cavity wall. It is lined by a layer of flattened to squamous epithelium. The epithelium lies on a wide zone of vascular granulation tissue.

FIG. 6D. Another view of the same cavity lined by flattened epithelium in one region and by a pyogenic membrane in another. Both lie on a wide zone of granulation tissue.

bacilli, the inspissated lesion in the left lung remained stable, and the patient was discharged from active hospital care. A follow-up report two years later revealed that the left lung lesion had remained stable, sputum cultures were negative for tubercle bacilli, and the pneumoperitoneum was being continued.

Pathologic findings: The resected lung measured 22 cm. apico-basally, 6 cm. mediolaterally, and 15 cm. anteroposteriorly. There were three cavities in the upper lobe varying in size from 2 to 6 cm. in diameter. They were lined by gray friable material and communicated freely with bronchi. A 3.5 cm. cavity was present in the superior and posterior aspects of the lower lobe. This cavity had a gray to gray-pink lining and communicated freely with a patent bronchus. Although much of the remaining lung parenchyma was resilient, there was a diffuse scattering of connective tissue, particularly in the upper lobe. Also present throughout the lung were small necrotic foci surrounded by well-defined capsules.

Microscopic examination revealed that the cavities in the right upper lobe were lined by a necrotic membrane surrounded by a wide layer of tuberculous granulation tissue. The cavity in the right lower lobe was lined in almost its entire aspect by a layer of flattened or squamous epithelium (figure 6*C*). In only small portions of its wall was there a pyogenic membrane (figure 6*D*).

Case 7: A 24-year-old white male was found to have pulmonary tuberculosis in December, 1949. A chest roentgenogram showed exudative infiltrations in the right first anterior interspace and in the left mid-lung field. Small cavities were suspected in these infiltrations. Laryngoscopic examination revealed early tuberculous involvement of the vocal cords.

In addition to bed rest, streptomycin, 1 gm. daily, and PAS, 9 gm. daily, were given from December 31, 1949, to February 2, 1950. Serial chest roentgenograms on July 3, 1950 revealed progression of the left-sided lesion. Accordingly, pneumoperitoneum was induced and streptomycin, 1 gm. every third day, and PAS, 9 gm. daily, were continued until September 15, 1950, when the patient was admitted to Brooklyn Veterans Administration Hospital.

Pneumoperitoneum was abandoned, but streptomycin, 1 gm. twice weekly, and daily PAS were continued. Bronchoscopy on September 24, 1950, indicated an essentially normal larynx and tracheobronchial tree. Sputum remained consistently positive for acid-fast bacilli and the patient continued to lose weight. Because of gastric intolerance, PAS was discontinued in November, 1950.

Left pneumothorax was induced November 22, 1950, and, although an adequate collapse was obtained, the cavities in the left upper lobe and left hilum region remained patent. Endobronchial disease was suspected despite negative bronchoscopic findings. Tomographic examination in January, 1951, revealed suspicious cavitation in the right upper lobe. The left pneumothorax was therefore abandoned and a right pneumothorax was induced in February, 1951. After the left lung had slowly re-expanded, considerable wheezing was frequently heard over that side.

In August, 1951, tomographic studies no longer revealed patent cavity in the collapsed right lung, and a Semb-type left thoracoplasty (eight ribs, two stages) was performed in an effort to control the extensive cavitary disease in that lung. This procedure failed to halt the relentless progression of the disease on the left side, the sputum remained positive for tubercle bacilli, and the patient steadily lost weight. Streptomycin was continued, 1 gm. twice weekly, and daily PAS was resumed in December, 1950. In March, 1952, drug susceptibility studies revealed the bacilli to be resistant to 10 and susceptible to 100 γ of streptomycin per ml. after a grand total of 210 gm. of streptomycin had been given over the preceding two and one-half-year period.

Streptomycin and PAS were discontinued and isoniazid, 300 mg. daily, was begun on March 6, 1952, with a fairly prompt symptomatic and objective response. Figure 7*A* indicates the extent of the disease at the time of institution of isoniazid therapy. There was marked decrease in cough, some decrease in expectoration, and by May 23, 1952, the patient

had gained ten pounds in weight. Viomycin, 2.0 gm. twice weekly, was begun and isoniazid was increased to 300 mg. daily in preparation for left pneumonectomy, which was performed on May 28, 1952. The procedure was well tolerated.

Pathologic findings: The left lung measured 18.5 cm. apico-basally, 11 cm. mediolaterally, and 4.5 cm. anteroposteriorly. A cavity measuring 3 by 2.5 by 1.5 cm. was present 4.5 cm. from the superior border and 2.5 cm. from the lat-

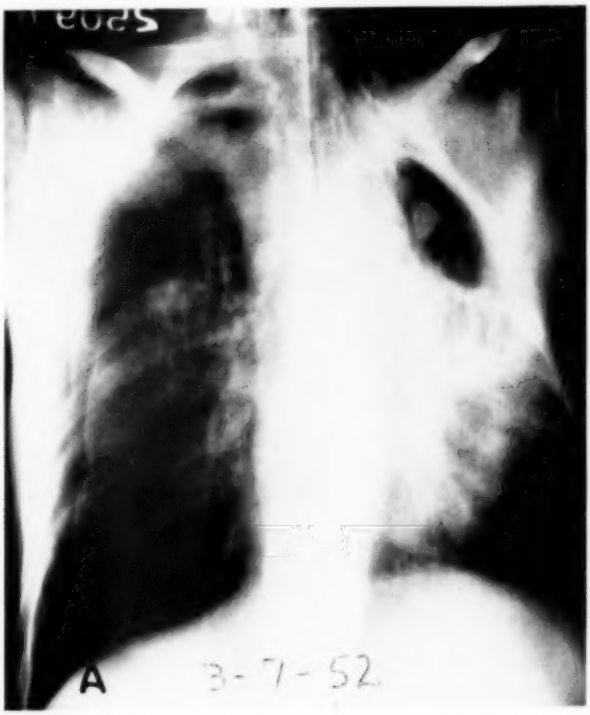


FIG. 7A. March 7, 1952. Tomogram. Multiple large cavities are present in left lung. Pneumothorax is present on the right.

eral pleura. The lumen was filled with soft yellow caseous material and communicated freely with bronchi. Oval and round necrotic foci measuring from 0.2 to 2 cm. were present throughout the remainder of the lobe, some appearing to be inspissated cavities. Similar foci were present in the left lower lobe, especially in the upper half.

Microscopic examination revealed that the upper lobe cavity was filled with necrotic debris which contained many neutrophils and calcium deposits. The inner wall was lined by a necrotic zone which terminated at the point where the epithelium formed the inner surface. Beyond the necrotic layer was vascular

granulation tissue surrounded by a wide layer of dense connective tissue. A branch of the upper lobe bronchus opened into the cavity. This bronchus was lined by tall columnar epithelium continuous with squamous epithelium along the inner wall of the cavity for a short distance (figure 7*B*). A smaller cavity with a draining bronchus was present in the left upper lobe. This showed changes similar to the larger cavity. The necrotic foci in both lobes showed ghost forms of underlying architecture within them. Many of these contained calcium salts and some

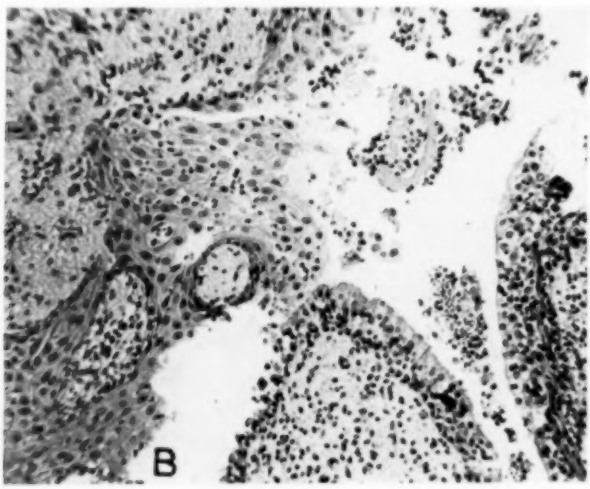


FIG. 7*B*. Photomicrograph of the bronchocavitary junction of the large cavity in left upper lobe. The bronchus in one area is lined by tall columnar epithelium which merges on either side with squamous epithelium. This epithelium lines the inner wall of the cavity for a short distance.

contained cholesterol crystals. These necrotic areas were surrounded by hyalinized connective tissue.

Case 8: A 58-year-old white male was admitted to Halloran Veterans Administration Hospital August 15, 1949, with a three-month history of productive cough of progressive severity, weight loss of approximately thirty pounds, left chest pain, profuse night sweats, intermittent small hemoptyses, and temperature elevation. Examination showed the temperature to be elevated to 104°F. Bronchovesicular breath sounds and many moist rales were heard over the region of the left upper lobe. A chest roentgenogram (figure 8*A*) revealed confluent and patchy infiltrations in the upper two-thirds of both lung fields and multiple areas of cavitation in both upper lobes. The sputum was positive for acid-fast bacilli on smear. The erythrocyte sedimentation rate was 37 mm. per hour.

The patient was treated symptomatically and with complete bed rest. Temperature gradually subsided, and he steadily gained weight. Pneumoperitoneum was induced on March 28, 1950, and was maintained by refills of 800 to 1,200 cc. weekly. Streptomycin, 1 gm. twice weekly, and PAS, 12 gm. daily, were started on November 11, 1950, and were continued to September 10, 1951; a total of 90 gm. He showed steady clinical improvement

as manifested by weight gain and decrease in severity of cough. Serial chest roentgenograms showed progressive clearing of the exudative infiltrations bilaterally. Nevertheless, the cavity in the left upper lobe progressively increased in size (figure 8*B*). Bronchoscopic examination on March 29, 1951, revealed an essentially normal tracheobronchial tree.

In view of the progressive increase in the size of the left upper lobe cavity, pneumoperitoneum was discontinued on March 23, 1951, one year after its induction. A two stage, seven-rib thoracoplasty was performed on April 5 and 27, 1951. The postoperative course was uneventful. He became completely asymptomatic, sputum reduced markedly in quantity and was only occasionally positive for tubercle bacilli. The cavity in the left upper lobe disappeared from view on serial roentgenograms.

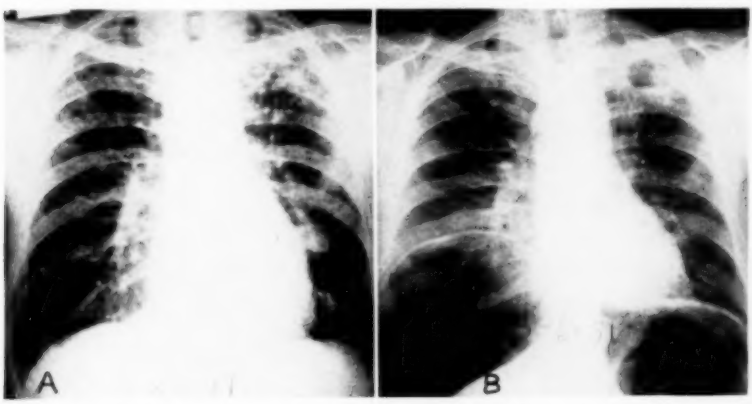


FIG. 8*A*. September 28, 1949. Confluent and patchy infiltrations are present in upper two-thirds of both lung fields, more marked on the left. Areas of cavitation are seen in left upper lobe; smaller cavities are also present in right upper lobe.

FIG. 8*B*. March 6, 1951. Marked clearing of infiltrations in both lung fields. Cavity in left upper lobe has increased in size. Pneumoperitoneum is present.

A second course of therapy with streptomycin, 1 gm. daily, and PAS, 12 gm. daily, was started April 14, 1952. On May 2, 1952, after a total dosage of 120 gm. of streptomycin, the left upper lobe was resected uneventfully. Drug susceptibility studies revealed the bacilli to be resistant to 10 and susceptible to 100 γ of streptomycin per ml. at this time.

Pathologic findings: The left upper lobe measured 17 cm. in the apico-basal direction, 9 cm. in the mediolateral direction, and 2 cm. in the anteroposterior direction. In the posterolateral aspect of the lobe and 2 cm. from the superior border was an inspissated cavity measuring 2 by 0.7 cm. A probe was easily passed from a branch of the left upper bronchus into the cavity. There were smaller yellow necrotic foci varying from 2 to 7 mm. surrounded by definite capsules.

Microscopic examination revealed that the lumen of the inspissated cavity was filled with necrotic material, in portions of which the former structure of the lung parenchyma was still discernible (figure 8*C*). At the bronchocavitary junction, the intact epithelial lining became continuous with a squamous layer extending along the inner wall for a short distance (figure 8*D*). The epithelial lining

terminated at a point where the inner wall of the cavity was lined by a necrotic zone. Beyond the necrotic layer of the cavity wall was a wide zone of tuberculous granulation tissue showing an abundance of collagen fibrils. There were other

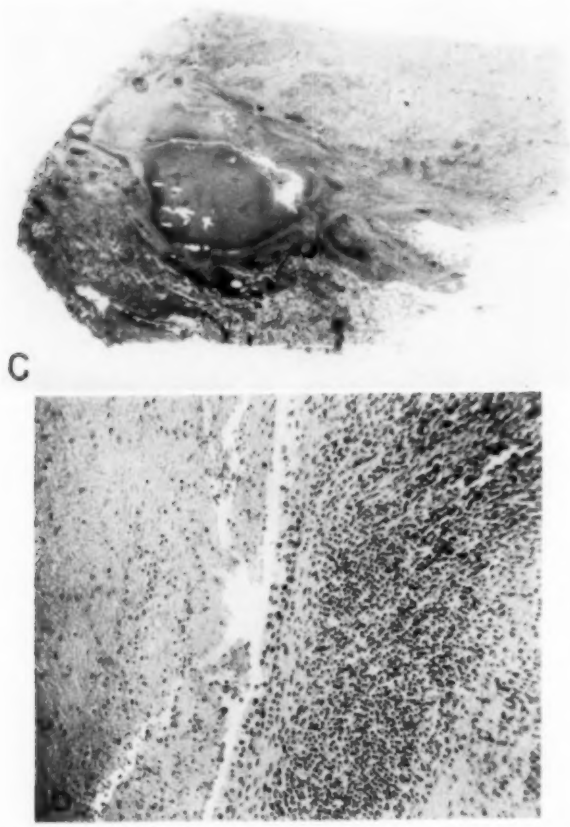


FIG. 8C. Photomicrograph of inspissated cavity showing a necrotic mass almost completely filling the lumen. A narrow necrotic zone lines the cavity.

FIG. 8D. Photomicrograph of the bronchocavitary junction showing the columnar epithelial lining of the bronchus becoming squamous as it extends on to the inner surface of the cavity. The lumen is filled with necrotic material which contains abundant neutrophils.

small zones of necrosis showing ghost forms of underlying lung parenchyma surrounded by concentrically arranged hyalinized connective tissue.

DISCUSSION

All of the cases in the present report had the following features in common: the bronchus at the bronchocavitary junction was lined by squamous or columnar

epithelium which extended along the cavity wall for some distance; there was a marked diminution in the size of the cavity; the cavity wall was in an advanced stage of anatomic healing; and the lung parenchyma immediately surrounding the cavity wall showed empty alveolar spaces, an indication that the perifocal reaction had been cleared by streptomycin.

The question naturally arises whether these changes resulted from streptomycin therapy or represented the natural evolution in the healing process of tuberculosis. In order to better evaluate these changes, findings in patients treated with streptomycin therapy were compared with those studied before the streptomycin era. The major portion of this pre-antibiotic case material was drawn from autopsy specimens. Consequently, the objection might be raised that the material is not comparable since the patients in the older series died as a result of progression of tuberculous disease. There is in this material a large comparable portion, however, namely, those cases in which the chronic pulmonary tuberculosis showed evidence of "clinical arrest" with anatomic healing although the patient died of amyloid uremia, extrapulmonary tuberculosis, or other complications unrelated to the primary pulmonary disease.

In a previous report (8), one of the writers showed that bronchi communicating with cavities almost invariably reveal the same tuberculous process as that seen in their respective cavities. Derscheid and Toussaint (9) have stated that it is not always possible to designate by gross or serial microscopic section the ending of the cavity and the beginning of the bronchus.

Like the cavity wall, the ulcerated surface of the bronchus may be lined by a necrotic caseous surface or a pyogenic membrane. The zone of granulation tissue beyond this inner layer is directly continuous with a similar one in the cavity. Generally the bronchocavitary junction is a tangential canal resulting in a check-valve mechanism at this site. As a result of this, more air enters the cavity during inspiration than leaves it during expiration, accounting for the usually constant spherical appearance of the cavity even though the areas of destroyed tissue are irregular in contour.

It is not difficult to conceive that there may be a proliferation of the endobronchial granulation tissue until apposing surfaces join and the lumen is obliterated. In cases in which closure does not occur, it is probable that continued infection of the granulating surface keeps pace with, or is perhaps ahead of, the proliferative processes of the granulation tissue, or continued tuberculous infection of the surface will not allow union between the apposing surfaces.

Collapse therapy may aid the process of bronchial occlusion either by producing distortion in the course of the bronchus or by actually collapsing the bronchial walls, if the extrabronchial pressure exceeds that of the intrabronchial pressure. The latter will result in apposition of the granulating surfaces, facilitating their union. If the granulating surfaces unite firmly, the occlusion will be lasting and the cavity permanently closed. It has been the experience of one of the writers (O. A.) that, in all instances of untreated cases in which inspissated cavities existed, the draining bronchi ended blindly either in the wall of the cavity or in an area of fibrosis connecting with the wall of the inspissated cavity.

Derscheid and Toussaint (9) believed that this area of fibrosis indicated the old path of the draining bronchus.

Coryllos (10) has emphasized that the development, behavior, and ultimate course of tuberculous cavities are inextricably bound to the pathologic and mechanical status of their draining bronchial outlets. He claimed that occlusion of draining bronchi is the initial and most essential factor in cavity closure and healing. This concept is further emphasized by the fact that, in nonstreptomycin-treated cases in which cavity closure and healing has occurred, microscopic examination of the bronchocavitary junction, even with serial sections, shows the draining bronchi to be obliterated, first by granulation tissue and later by scar formation.

Following closure of the bronchi, air is absorbed from the lumen of the cavity and the cavity wall contracts quite rapidly. Since most cavities contain large necrotic masses within the lumen and along the inner wall, these become inspissated and form the core of the obliterated cavity. The soft caseous material becomes firmer in consistency with absorption of its fluid content. In time, calcium is deposited in the necrotic center. Simultaneously, the wall of the cavity, through an increase of collagen fibrils, is converted into a zone of hyalinized connective tissue. Invariably, the caseous contents within the inspissated cavity can be washed out when immersed in water, even in patients with advanced stages of healing with calcification. Although healed cavities with inspissation of the caseous contents have been reported with a fair degree of frequency (8, 9, 11–13), there is no unanimity of opinion that these are always the result of the sealing-off of the bronchus at the bronchocavitary junction (14–16).

In a review of more than 2,000 autopsies of chronic pulmonary tuberculous patients who received no antibiotic therapy during their illness, the present writers have observed only one case of extensive re-epithelialization of the cavity walls. Tubercle bacilli disappeared from the sputum nine years before the patient's death, and the annular shadows corresponding to the cavities persisted in roentgenograms (8). This is in general agreement with the observations of previous authors. Pinner (17) stated that epithelialization of a clean cavity wall is extremely rare and occurs only in minute cavities. Huebschmann (18) never observed epithelialization of an "open" healed cavity, although he did not doubt that it might occur. It is of interest that Meissner and associates (19), in a study of the pathology of resected lungs in 62 cases of thoracoplasty failures, found one instance in which there was an epithelialized cavity showing no evidence of active tuberculosis. The present writers have encountered partial re-epithelialization in approximately 4.5 per cent of nonstreptomycin-treated cases of chronic pulmonary tuberculosis observed at autopsy. This figure is not considered to have statistical validity since the entire circumference of the cavity wall was not studied. Two general impressions have resulted from a study of the material: (*1*) The frequency of epithelialization increased in proportion to the chronicity of cavities; (*2*) the bronchi leading into the cavity were wider at the bronchocavitary junction. Less chronic cavities communicating with both the external surface and the bronchi, either as a result of bronchopulmonary-cutaneous

fistula or surgical cavernostomy, invariably showed variable degrees of epithelialization of the cavity wall. Cases of partial epithelialization of the cavity wall following the development of a bronchopulmonary-cutaneous fistula have been observed by Pagel (20) and Koch (21). The impression is gained from the above findings that partial epithelialization of a cavity occurs when a cavity wall can more easily drain its necrotic contents, either through a more widely patent bronchus at the bronchocavitary junction or through patent skin fistulas. Contact with outside air appears to be a factor since cavities communicating with bronchopleural fistulas showed no greater frequency of epithelialization in the absence of cutaneous communication.

A feature of epithelialization in nonstreptomycin-treated cases is lack of continuity of epithelium from the bronchus along the inner surface of the cavity. The epithelium which is columnar or squamous in character, more frequently the latter, lies on a zone of granulation tissue; never on an underlying pyogenic or caseous layer. The epithelium which lies along any part of the cavity wall must arise from a re-epithelialization at the bronchocavitary junction. In the ordinary course of events, the tuberculous process of cavitation is one of progression and healing which occur simultaneously. Thus, after re-epithelialization has occurred in part of a cavity wall, a caseous focus adjacent to it may liquefy and empty its contents into the lumen. Should this perforation occur in the proximal aspect at the site of epithelialization, the part of the epithelium thus involved will either be lifted off by the underlying liquefied necrotic zone or become involved in the necrotic process. The more distal portion of the epithelium will remain intact and the continuity with the adjoining re-epithelialized bronchial wall will be interrupted by the zone of caseation lining the cavity wall at this site.

In "open" healing without re-epithelialization in nonstreptomycin-treated cases, the cavity wall is transformed into a dense zone of connective tissue with dense coal pigment deposition with loss of all signs of specificity. The necrotic contents within the lumen of the cavity are evacuated, and the lining is either desquamated or organized into dense connective tissue. Only one such instance has been observed in the writers' autopsy series. The patient had had chronic pulmonary tuberculosis for fourteen years prior to her death from amyloid uremia. Tubercle bacilli disappeared from the sputum four years before her death. Autopsy showed that the cavity lumen was patent and its wall had been transformed into a zone of connective tissue in which all signs of specificity had disappeared. There was no evidence of epithelium in any part of the cavity wall. It is noteworthy that this form of cavity healing has most frequently been described in the literature (18, 22–28). This emphasizes the fact that in cavity healing in the presence of a patent bronchus there is much less tendency for epithelium to line the cavity wall.

It is the impression of the present writers that streptomycin generally exerts its most beneficial effect on lesions of surfaces. This effect, however, persists only as long as the organisms remain streptomycin-susceptible. This favorable action on tuberculous lesions of surfaces is strikingly evident in healing of sinus

tracts. Another example of this action is the absence of intestinal and laryngotracheobronchial lesions at autopsy in patients with organisms still susceptible to the drug at, or shortly before, death. The significance of this is appreciated when compared with nonstreptomycin-treated cases in which intestinal tuberculosis occurs in more than 70 and laryngeal tuberculosis in more than 40 per cent.

At the present time there is an increased opportunity to study the effects of streptomycin on the bronchocavitary junction for two reasons: (*1*) Since the addition of PAS, the beneficial effects of streptomycin therapy have been greatly prolonged; (*2*) there is presently a tendency to resect lesions after prolonged chemotherapy, although tubercle bacilli have disappeared from the sputum and the cavity has become lost to view on conventional roentgenograms.

All cases in the present series showed re-epithelialization of the bronchus at the bronchocavitary junction with extension along the inner wall of the cavity to a variable degree. In one case the re-epithelialization extended along almost the entire inner surface of the cavity. In all cases the cavity decreased in size and was inspissated with caseous material except in the case noted above.

Two significant questions arise: what are the conditions leading to decrease in size of cavity with inspissation of its caseous contents; and what are the factors determining the extent of epithelialization of the cavity wall?

It is possible that the ulcerative process of the bronchus and its tangential entrance into the cavity are responsible for a check-valve mechanism at the bronchocavitary junction which allows more air to enter than to leave the cavity. Thus, a distended cavity lined by variably wide zones of caseation results. Apparently as a result of streptomycin, the necrotic surface of the bronchial ulcer is denuded and re-epithelialization occurs by regeneration from intact epithelium. This re-epithelialization now disrupts the check-valve mechanism so that distension of the cavity no longer occurs, and contraction of granulation tissue in its wall results in decreased size of cavity. As the granulation tissue contracts, the caseous contents within the cavity lumen become inspissated. The fluid within the necrotic debris is absorbed. As the process of healing continues, calcium salts are deposited in the necrotic zone and the zone of granulation tissue is gradually converted into hyaline connective tissue.

The end result in these cases is an inspissated cavity with a communicating bronchus. The epithelium from the bronchus extends along the inner wall of the cavity for a variable distance. Comparing the healed cavity after streptomycin therapy with that healed without streptomycin it is found that in treated cases the bronchus is patent, while in untreated cases no bronchial communication can be demonstrated.

In this connection, Case 8 is of importance and interest. Re-epithelialization at the bronchocavitary junction prevented cavity closure and thus may have accounted for the failure of thoracoplasty. Although the contents of the residual cavity were completely inspissated, and the cavity disappeared from view on serial conventional as well as on tomographic roentgenograms, the sputum remained intermittently positive for tubercle bacilli. Previous experience with

thoracoplasty in the pre-streptomycin era indicates that complete inspissation of cavity contents with disappearance of cavity from tomographic view is invariably associated with "conversion" of sputum. It therefore appears that, in this particular case, re-epithelialization at the bronchocavitary junction which resulted from streptomycin had an adverse effect in that it contributed to thoracoplasty failure.

Is the inspissated cavity with a patent bronchus a potential source of danger? This depends upon the fate of the tubercle bacilli in the inspissated cavity in patients undergoing prolonged combined chemotherapy. D'Esopo and associates (29) have described the effects of long-term combined therapy on bacilli in such lesions. They found that, in patients treated for eight months or longer with daily streptomycin-PAS in whom the cavity disappeared from roentgenographic view, they could neither grow cultures of tubercle bacilli nor produce disease in the guinea pig inoculated with contents of excised inspissated cavities. Smears from these lesions invariably showed acid-fast organisms, often in great numbers. These writers concluded that in such lesions the tubercle bacilli are not viable. They further emphasize the selected nature of this clinical material: the fact that resections were performed only after closure of cavities on planigrams, maximal resolution of disease, eight months or more of combined therapy, and sputum consistently negative for tubercle bacilli on culture. If the bacilli in these lesions are not viable, it appears likely that factors other than drug action alone must be responsible for their death since in patients receiving similar chemotherapeutic regimens whose cavities remain open there was no difficulty in growing tubercle bacilli from the cavity contents after excision (29). The failure to culture bacilli from an inspissated cavity is not unique to streptomycin-treated cases. The present writers have recently observed a patient with spontaneous closure of cavity and complete inspissation of its contents. Smear of the necrotic contents was positive, but a culture of this material was negative for tubercle bacilli.

Dubos (30) emphasized that the tuberculocidal effect in inspissated caseous lesions is the result of the physicochemical environment which prevails within these lesions. Since tubercle bacilli are obligatory aerobes, oxygen deprivation is an important factor in causing the death of the bacilli. It would appear, then, that patency of the bronchocavitary junction serves as a pathway for free access of oxygen to the bacilli within the cavity and thus maintains the viability of the organisms. Dubos indicated, however, that additional factors in the physicochemical environment determine the survival and rate of multiplication of the bacilli. The presence of lactic acid, long-chain fatty acids, and other tuberculostatic substances within the caseous material exerts a deleterious effect on tubercle bacilli and interferes with their survival.

If the bacilli in the inspissated cavities of streptomycin-treated patients should prove to be viable after discontinuation of therapy, it would seem hazardous to leave such lesions *in situ*. The possibility must be considered that, if the bacilli were again to multiply within these inspissated lesions, reactivation of disease would occur. Such patients subjected to re-treatment would be expected to de-

velop streptomycin resistance rapidly. Should bacilli remain viable within residual inspissated lesions, it would be imperative that the indications for prolonged chemotherapy be carefully evaluated.

If the findings of D'Esopo and associates (29) prove that the inspissated cavities with open bronchi are not a source of future danger, then the question arises concerning the ultimate fate of the inspissated cavity. Several possibilities can be visualized. The caseous contents may become completely calcified and will then remain as a hard mass within the capsule. Another possibility is that the necrotic fragments may be evacuated from the lumen of the cavity through the patent bronchus. This would then mean that at some future time an annular shadow would again appear at the site of an old cavity. The wall of the cavity would be composed of dense hyalinized connective tissue. As the caseous contents are evacuated, it would be possible for the epithelium to continue to regenerate along the inner surface of the wall until it is completely relined. As the caseous contents are evacuated it is possible that some of the material might be aspirated and result in the formation of foreign-body granuloma or bronchopneumonia. Another possibility which the writers have observed is the invasion of the necrotic contents by polymorphonuclear leukocytes and the subsequent late liquefaction of the inspissated cavity.

SUMMARY

The essential difference between cavity closure in streptomycin-treated and untreated cases is that, in the former situation, there is re-epithelialization of the bronchus at the bronchocavitary junction and the lumen of the bronchus remains patent; in the latter circumstance, there is permanent obliteration of the bronchus at the bronchocavitary junction.

The bronchocavitary junction in streptomycin-treated cases shows re-epithelialization of varying extent. In some instances, this epithelium extends far around the inner cavity wall. Generally, the epithelium is flattened or squamous in character; occasionally, it is columnar.

Epithelialization at the bronchocavitary junction prevents obliteration of the bronchial lumen at this site, an important factor in preventing permanent closure of the corresponding cavity.

The lumen of such cavities is greatly diminished in size and their contents become inspissated. Calcium may be deposited within the necrotic center.

The potential dangers inherent in such inspissated lesions with patent, re-epithelialized draining bronchi have not yet been precisely defined. As a consequence, it is not yet possible to determine whether such unobliterated residual cavitary foci should be left *in situ* or whether resection of such areas is obligatory.

SUMARIO

El Efecto de la Estreptomicinoterapia sobre la Unión Broncocavitaria y su Relación con la Cicatrización de las Cavernas

La diferencia fundamental en el cierre de las cavernas entre los casos tratados con estreptomicina y los no tratados radica en que, en los primeros, hay re-epitelialización del

bronquio en la unión broncocavernosa y la luz del bronquio permanece permeable; en los segundos, hay obliteración permanente del bronquio en dicha unión.

En los casos tratados con estreptomicina, la unión broncocavitaria revela más o menos re-epitelialización. En algunos, ese epitelio se extiende bien lejos alrededor de la pared interna de la caverna. Generalmente, el epitelio toma forma aplanada o escamosa; de vez en cuando, es cilíndrico.

La epitelialización en la unión broncocavitaria impide la obliteración de la luz del bronquio en dicho punto, factor este importante en lo tocante a impedir la clausura permanente de la caverna correspondiente.

La luz de esas cavernas disminuye mucho de tamaño y el contenido de las mismas se espesa, pudiendo depositarse calcio en el centro esfacelado.

Se exponen los peligros potenciales que entrañan esas lesiones espesadas con bronquios de drenaje permeables y re-epitelializados.

¿Pueden dejarse *in situ* esos focos cavernosos residuales inobliterados o es obligatoria la resección de dichas zonas?

RESUME

Effet de la streptomycinothérapie sur la jonction broncho-cavitaire et sa relation avec la cicatrisation des cavernes

La différence essentielle entre l'oblitération des cavernes dans les cas traités par la streptomycine, ou non traités, est que dans le premier cas il y a une ré-épithélisation de la bronche à la jonction broncho-cavitaire avec persistance de la lumière du canal bronchique; dans le deuxième cas, il se produit une oblitération permanente de la bronche à la jonction broncho-cavitaire.

Dans les cas traités par la streptomycine, la jonction broncho-cavitaire présente une ré-épithélisation de degrés variés. Dans certains cas, cet épithélium s'étend très loin autour de la paroi interne de la caverne. En général, l'épithélium est du type plat ou pavimenteux et parfois cylindrique.

L'épithélisation au niveau de la jonction broncho-cavitaire prévient l'oblitération de la lumière bronchique en ce point, ce qui est un facteur important dans la prévention de l'occlusion permanente de la caverne correspondante.

La lumière de ces cavités est considérablement diminuée et le contenu de la caverne se dessèche. Un dépot de calcium peut se produire au centre des tissus nécrosés.

Le potentiel de danger que représente de telles lésions desséchées, comportant des bronches de drainage ré-épithélisées et non oblitérées, a été étudié.

Ces foyers cavitaires résiduels non oblitérés doivent-ils être laissés *in situ* ou leur résection est-elle une nécessité?

REFERENCES

(1) Hinshaw, H. C., Feldman, W. H., and Pfuetze, K. H.: Treatment of tuberculosis with streptomycin, J.A.M.A., 1946, *138*, 778.

(2) Kidd, J. G.: Modifications of tuberculous lesions in patients treated with streptomycin, Bull. N. Y. Acad. Med., 1948, *24*, 132.

(3) Auerbach, O., and Stemmermann, G. N.: Anatomic changes in tuberculosis following streptomycin therapy. Am. Rev. Tuberc., 1948, *58*, 449.

(4) Mahon, H. W.: Pathology of tuberculosis as modified by streptomycin therapy, Am. Rev. Tuberc., 1950, *61*, 543.

(5) Silverthorne, M. C., and Silverman, G.: The effect of streptomycin on the morphology of the tuberculous lesion, Am. Rev. Tuberc., 1950, *61*, 525.

(6) Auerbach, O., Weiss, L., and Stemmermann, G. N.: Pathology of tuberculosis treated with streptomycin: A review of 34 cases, Dis. of Chest, 1951, *19*, 145.

(7) Silverman, G., Klopstock, R., and Gibbons, G.: The surgical pathology of pulmonary tuberculosis, Dis. of Chest, 1952, *86*, 21.

(8) Auerbach, O., and Green, H.: The pathology of clinically healed tuberculous cavities, Am. Rev. Tuberc., 1940, *42*, 707.

(9) Derscheid, G., and Toussaint, P.: Necroses tuberculeuses et cavernes pulmonaires, processus de guérison, Presse méd., 1937, *45*, 1739.

(10) Coryllos, P. N.: How do rest and collapse treatment cure pulmonary tuberculosis, J.A.M.A., 1933, *100*, 430.

(11) Hart, C.: Über die Heilbarkeit und Heilung tuberkulöser Lungenkavernen, Ztschr. f. Tuberk., 1922, *35*, 253.

(12) Amberson, J. B.: The process of resolution in pulmonary tuberculosis, Am. Rev. Tuberc., 1936, *33*, 269.

(13) Pagel, W., and Simmonds, M. A.: The healing of cavities, Am. J. M. Sc., 1939, *197*, 281.

(14) Bronkhorst, W.: Neue Deutungen der Kavernenheilung, Beitr. z. Klin. Tuberk., 1929, *72*, 36.

(15) Salkin, D., Cadden, A. V., and McIndoe, R. B.: The blocked pulmonary cavity, Am. Rev. Tuberc., 1936, *34*, 634.

(16) Jacquerod, M.: The Natural Processes of Healing in Pulmonary Tuberculosis, translated by J. D. Sinclair, William Wood and Co., New York, 1926.

(17) Pinner, M.: Pathology of pulmonary collapse, in John Alexander's *The Collapse Therapy of Pulmonary Tuberculosis*, Charles C Thomas, Springfield, Illinois, 1937.

(18) Huebschmann, P.: Pathologische Anatomie der Tuberkulose, Julius Springer, Berlin, 1928.

(19) Meissner, W. A., Overholt, R. H., Wilson, N. J., and Walker, J. H.: The resected post-thoracoplasty lung, Am. Rev. Tuberc., 1949, *60*, 406.

(20) Pagel, W.: Zur Enstehungsgeschichte und Kasuistik der Lungentuberkulose, Beitr. z. Klin. Tuberk., 1931–1932, *79*, 383.

(21) Koch, O.: Pathologische anatomische Beobachtungen zur Frage der "offenen" und "geschlossenen" Kavernenbehandlung, Ztschr. f. Tuberk., 1938, *80*, 1.

(22) Alexander, H.: Zum Problem der tuberkulösen Kaverne, Beitr. z. Klin. Tuberk., 1935, *86*, 424.

(23) Fisher, B.: Über Ausheilung grosser tuberkulöser Lungenkavernen, Beitr. z. Klin. Tuberk., 1903, *1*, 153.

(24) Giegler, G.: Über die Vorgänge der Reinigung und Heilung der Kavernen bei der Lungenphthise und deren prognostische Bedeutung, Beitr. z. Klin. Tuberk., 1924–1925, *60*, 195.

(25) Graeff, S.: Die Kaverne der Lungentuberkulose vom pathologisch-anatomischen Standpunkt aus, Ergebn. d. ges. Tuberk-Forsch., 1935, *7*, 257.

(26) Hansemann, D.: Über Heilung und Heilbarkeit der Lungenphthise, Berl. klin. Wchnschr., 1902, *39*, 745.

(27) Orth, J.: Einige Bemerkungen zur Frage der Heilbarkeit tuberkulöser Lungenkavernen, Ztschr. f. Tuberk., 1921, *35*, 251.

(28) Pagel, W., and Robinson, H. J.: Spontaneous cavity healing, Papworth Research Bull., 1936, *1*, 37.

(29) D'Esopo, N. D., Bernstein, S., Lee, W. F., Decker, A. M., and Steenken, W., Jr.: The bacteriology of resected lesions during chemotherapy, Tr. Eleventh Conference on the Chemotherapy of Tuberculosis, January 17 to 20, 1952, St. Louis, Missouri.

(30) Dubos, R. J.: Discussion on treatment of tuberculous meningitis and survival of bacilli in tuberculous lesions (notes), Am. Rev. Tuberc., 1952, *65*, 637.

THE EFFECT OF CORTICOTROPIN (ACTH), DIHYDROSTREPTOMYCIN, AND CORTICOTROPIN–DIHYDROSTREPTOMYCIN ON EXPERIMENTAL BOVINE TUBERCULOSIS IN THE RABBIT[1]

JAMES M. BACOS[2] AND DAVID T. SMITH

(Received for publication August 13, 1952)

INTRODUCTION

Corticotropin (ACTH) and cortisone abolish or materially reduce the reaction to the tuberculin skin test in man (1–4) and animals (5–7). The hormones reduce fever and inhibit other constitutional symptoms when administered to patients with severe active tuberculosis. Their employment in certain types of tuberculosis would be advantageous provided the disease itself was not unfavorably influenced by other effects of the hormones.

The administration of cortisone to mice (8), rats (9, 10), guinea pigs (11), and rabbits (7) infected with tubercle bacilli was proved to be deleterious since the treated animals were found to have more extensive disease than the controls (12). Patients treated with cortisone for rheumatoid arthritis and other diseases not infrequently develop progressive tuberculosis (13–17). The available evidence suggests that cortisone may reduce resistance to tuberculosis.

Patients with pulmonary and laryngeal tuberculosis show dramatic improvement following corticotropin (ACTH) therapy but relapse when the hormone is withdrawn suddenly (2, 3), although they may eventually recover following streptomycin therapy (4). The results obtained by Wallner, Thompson, and Lichtenstein (18) were less dramatic than those of LeMaistre and his associates (3). There is a possibility that ACTH will not have as deleterious an effect on infections as cortisone. This has been demonstrated with certain viral infections (19–21) and with tuberculosis in the guinea pig (22) and rat (23). In contrast, Bunn and Drobeck (24) found ACTH more deleterious than cortisone in experimental ocular tuberculosis in the rabbit.

A previous study in this laboratory (25) showed that ACTH would prevent the development of necrosis in tuberculin-sensitive rabbits following the intratracheal injection of undiluted Old Tuberculin. The present study was designed to ascertain the effect of corticotropin, dihydrostreptomycin, and the combination of corticotropin and dihydrostreptomycin on the course of experimental pulmonary tuberculosis in previously sensitized and presumably partially immunized rabbits.

MATERIALS AND METHODS

Sixty-six rabbits, including animals of both sexes, weighing between 2,000 and 3,000 gm. were sensitized to tuberculin by the subcutaneous injection of 1 ml.

[1] From the Department of Bacteriology, Duke University School of Medicine, Durham, North Carolina.

[2] Frederick M. Hanes Research Fellow.

of a homogeneous suspension of living avirulent tubercle bacilli (*Mycobacterium tuberculosis* R1v Saranac strain). Thirty to forty days were allowed for sensitivity to develop, after which the rabbits were used in three separate experiments.

Experiment I: Twenty-three sensitized rabbits were etherized, the trachea of each was exposed, and 5 mg. of the Ravenel bovine Saranac strain of *Mycobacterium tuberculosis* suspended in 0.25 ml. of physiologic saline were injected with a tuberculin syringe and a 24-gauge hypodermic needle. Each rabbit was held on its right side with the head raised to allow the suspension of tubercle bacilli to flow into the right upper lobe. Each of 11 rabbits was given 2.5 mg. of corticotropin (ACTH)[3] every six hours to make a total daily dose of 10 mg. or approximately 5 mg. per kg. of weight. The first dose of ACTH was given six hours prior to the injection of the tubercle bacilli. Six of the 11 rabbits were given supplementary treatment with dihydrostreptomycin, 15 mg. every six hours, for a total of 60 mg. daily, or approximately 30 mg. per kg. of body weight. Five rabbits received dihydrostreptomycin without ACTH and 7 remained untreated and served as controls. One animal from each of the four groups was sacrificed after four days. An additional animal from the dihydrostreptomycin therapy group was sacrificed on the sixth day.

After ten days of therapy, the dose of ACTH was reduced to 2.5 mg. every twelve hours, or a total of 5 mg. daily. The dose of ACTH after twenty days of therapy was reduced to 2.5 mg. once each day and the amount of dihydrostreptomycin was reduced to 30 mg. per day. After the thirtieth day the ACTH dose was limited to a single injection of 1.25 mg. daily and that of dihydrostreptomycin to a single dose of 30 mg. daily. The experiment was terminated after 120 days.

The lungs of the animals which died during the experiment or were sacrificed at its termination were photographed in black and white and in color, after which they were fixed in Helly's solution. Representative areas were sectioned and stained with hematoxylin and eosin and also with carbolfuchsin and methylene blue for tubercle bacilli.

Experiment II: Twenty sensitized rabbits were infected, divided equally into four groups and treated as in *Experiment I*. The infecting dose was 4 mg. of tubercle bacilli and the experiment was terminated after eighty days.

Experiment III: Twenty-three sensitized rabbits were injected intratracheally with 4 mg. of tubercle bacilli. Six animals were treated with dihydrostreptomycin; 6 were treated with dihydrostreptomycin and ACTH; 6 were treated with ACTH; and the remaining 5 were untreated and served as controls. The dosages used were identical to those used in *Experiment I*. All of these animals were sacrificed after six days of treatment.

RESULTS

Experiment I: One animal from each group was sacrificed after four days of treatment. In each animal, infiltration characteristic of a pneumonic process was found, usually in the right upper lobe. In the untreated control animal, a dark hemorrhagic area around the zone of infiltration was present; however, the degree of hemorrhage and necrosis was much less extensive with 5 mg. of bacilli than with 0.25 ml. of undiluted tuberculin (25). The rabbit which received corticotropin and the one which received both ACTH and dihydrostreptomycin had areas of pneumonic infiltration without hemorrhage or obvious necrosis. The animal

[3] The ACTH used in these experiments was furnished through the courtesy of Mr. Irby Bunding, Armour and Company, Chicago, Illinois.

which received dihydrostreptomycin without ACTH had an area of bright hemorrhagic reaction about the zones of infiltration. The lungs of a second animal sacrificed from this group on the sixth day of the experiment also revealed a bright hemorrhagic reaction.

One of the untreated control rabbits died on the eighty-ninth day, another on the ninety-ninth day, and a third on the one hundred and first day of the experiment. The lungs of these animals as well as those of the remaining 3 which were sacrificed at the termination of the experiment exhibited characteristic fibrocaseous tuberculosis with hemorrhagic areas about the zone of infiltration. A photograph of the control rabbit which died on the ninety-ninth day is shown in plate I, figure 1. Microscopic sections from this lung are shown in plate II, figures 3 and 7. Few tubercle bacilli were found, but giant cell formations were numerous, as well as massive confluent areas of necrosis surrounded by areas of fibroblastic proliferation (plate II, figure 7).

One animal which received ACTH died on the fifty-sixth day of the experiment and was accidently incinerated by the caretaker before necropsy could be performed. A second animal in this group died on the one hundred and nineteenth day, and necropsy showed the presence of extensive pulmonary tuberculosis. The remaining animals which received ACTH were sacrificed at the termination of the experiment on the one hundred and twentieth day. The lungs were somewhat smaller than normal and all showed dense nodular lesions scattered throughout all lobes as shown in plate I, figure 3. Microscopic sections from this lung can be seen in plate II, figures 1, 4, and 5. The lesions contained a preponderance of large mononuclear cells, many of which were filled with tubercle bacilli (plate II, figure 5). Isolated areas of minimal necrosis and clusters of lymphocytes were present. Conspicuously absent were the hemorrhage, necrosis, giant cells, and fibroblastic formation which characterized the pathologic process in the lungs of the untreated animals.

None of the remaining 3 animals which received dihydrostreptomycin died during the experiment. When sacrificed on the one hundred and twentieth day the lungs of one animal were apparently normal, while the other 2 had extensive disease. Not all of the lobes were infected but the gross and microscopic appearance of the involved areas was identical with that found in the untreated controls. It was assumed but not proved that the bacilli in these rabbits had become resistant to dihydrostreptomycin.

None of the remaining animals which were treated with both ACTH and dihydrostreptomycin died during the experiment. When sacrificed on the one hundred and twentieth day, 4 of the 5 animals had apparently normal lungs. One rabbit showed a small scarred area in the right upper lobe and a few questionable areas of infiltration in the left upper lobe (plate I, figure 4). Microscopic sections (plate II, figures 2 and 6) revealed the healing residue of a more extensive lesion. The primary cellular reaction was an accumulation of large vacuolated mononuclear cells comparable to those seen in the animals which received ACTH without dihydrostreptomycin. However, these two groups differed sharply in the number of tubercle bacilli being harbored within the cells since only after a prolonged

search were a few bacilli found in the lungs of those rabbits which received ACTH and dihydrostreptomycin.

Experiment II: The 20 sensitized animals in this experiment were infected with 4 mg. of tubercle bacilli, divided into groups, and treated as in *Experiment I*. One animal from each group was sacrificed on the fourth and sixth days of the experiment. There were no spontaneous deaths, and the remaining animals were sacrificed on the eightieth day of the experiment.

All of the controls had extensive fibrocaseous tuberculosis throughout all lobes of the lungs. Two of the 3 animals which received dihydrostreptomycin had extensive disease, while the lungs of the remaining animal were apparently normal. All 3 animals which received ACTH had small nodular lesions scattered through all of the lobes. Two of the 3 animals which received both ACTH and dihydrostreptomycin had apparently normal lungs, while the third showed a single small area of infiltration.

Experiment III: The bright hemorrhagic reaction observed in the 2 rabbits which were treated with dihydrostreptomycin and sacrificed on the fourth and sixth days of the experiment suggested the possibility of a Herxheimer-like reaction caused by the liberation of tuberculoprotein from tubercle bacilli destroyed by dihydrostreptomycin. The absence of this type of reaction in the animals which received both ACTH and dihydrostreptomycin suggests suppression of this reaction by the hormone. In *Experiment III*, 6 sensitized rabbits were treated with dihydrostreptomycin; 6 were treated with dihydrostreptomycin and corticotropin; 6 received corticotropin; and the remaining 5 were untreated. All 6 of those animals which received dihydrostreptomycin displayed greater hemorrhagic involvement than any of the animals comprising the other groups.

DISCUSSION

The significance of these observations will be apparent when the entire series is summarized.

Sixty-six rabbits were sensitized by the subcutaneous injection of the avirulent *Mycobacterium tuberculosis* R1v strain. The animals were anesthetized with ether, the trachea was surgically exposed, and either 4 or 5 mg. of virulent bovine tubercle bacilli (Ravenel strain), suspended in 0.25 ml. of physiologic saline, were injected in such a manner as to facilitate localization of the bacilli in the right upper lobe. Twelve animals received no specific treatment and served as controls. Ten rabbits were treated with corticotropin, beginning with an initial dose of 2.5 mg. every six hours. At successive ten-day periods this dose was reduced to 2.5 mg. every twelve hours and 2.5 mg. every twenty-four hours until the thirtieth day, at which time 1.25 mg. every twenty-four hours were given for the remainder of the experiment. Ten rabbits received dihydrostreptomycin (60 mg. daily for twenty days and then 30 mg. daily until the end of the experiment). Eleven animals received both ACTH and dihydrostreptomycin simultaneously in the doses recorded above. The first series of experiments was terminated on the one hundred and twentieth day and the second on the eightieth day.

In the third series of experiments, 18 rabbits were divided equally into three groups and received ACTH, dihydrostreptomycin and ACTH, and dihydrostreptomycin, respectively, employing the initial dosages noted above. An additional 5 rabbits remained untreated. All 23 animals were sacrificed after the sixth day.

The initial reaction to the intratracheal injection of either 4 or 5 mg. of bovine tubercle bacilli was analogous to, but somewhat less intense than, that produced by 0.25 ml. of undiluted Old Tuberculin. Corticotropin eliminated the hemorrhagic type of reaction but did not prevent pulmonary infiltration. Dihydrostreptomycin apparently increased the intensity of the hemorrhagic type of reaction between the fourth and sixth days of treatment, presumably by accelerating the destruction of tubercle bacilli and increasing the available tuberculoprotein. This Herxheimer-like type of reaction was prevented in the group of rabbits in which the dihydrostreptomycin was supplemented by ACTH.

All of the remaining 9 untreated control animals either died of tuberculosis during the course of the experiment or had extensive disease when sacrificed. Of the 8 remaining animals which were treated with decreasing doses of ACTH, one died and was discarded before it could be examined; one died of extensive disease on the one hundred and nineteenth day; and the remaining 6, although they survived until the one hundred and twentieth day, were found to have numerous small nodular lesions throughout all lobes of the lungs when sacrificed. The lungs of these animals were less voluminous than the controls, with conspicuous absence of the usual hemorrhagic tuberculin-like reaction surrounding the lesions and only minimal caseation, few giant cells, and no fibroblasts. Nevertheless, the numerous large mononuclear cells in the infected area were often filled with tubercle bacilli. Two of the remaining 6 animals which were treated with dihydrostreptomycin had normal lungs at the termination of the experiment; however, the other 4 revealed cellular changes which were similar to, though somewhat less extensive than, the controls. Seven of the 9 remaining animals which were treated simultaneously with ACTH and dihydrostreptomycin had normal lungs at the end of the experiment. The remaining animals had small residual areas of infection.

In contrast to the unfavorable reports in the literature concerning the effects of cortisone on experimental tuberculosis in the rabbit, the animals which received corticotropin did not die sooner than the controls and showed less, rather than more, disease at necropsy. The presence of extensive tuberculosis in 4 of the 6 remaining animals which were treated with adequate doses of dihydrostreptomycin was assumed to be the result of the emergence of dihydrostreptomycin-resistant strains. This is an assumption, however, since the microorganisms were not isolated and tested for drug resistance. The absence of progressive disease in all animals which received simultaneous treatment with both corticotropin and dihydrostreptomycin suggests that the hormone may have delayed the appearance of resistant strains. However, this conclusion cannot be drawn from the present experiments because such a distribution might have occurred by chance in a group of 66 animals.

The present experiments indicate that corticotropin does not materially reduce

the resistance of previously sensitized rabbits to tuberculosis and that it can be administered with safety if dihydrostreptomycin is given simultaneously.

SUMMARY

Sixty-six rabbits were sensitized by the subcutaneous injection of the avirulent *Mycobacterium tuberculosis* R1v strain, after which they were infected intratracheally with 0.25 ml. of the Ravenel strain of the bovine tubercle bacillus. All 12 of the untreated control animals developed extensive progressive tuberculosis. Ten animals received corticotropin (ACTH), beginning with an initial dose of 2.5 mg. every six hours. At successive ten-day periods the dose was reduced to 2.5 mg. every twelve hours and 2.5 mg. every twenty-four hours until the thirtieth day, at which time 1.25 mg. every twenty-four hours was continued for the remainder of the experiment. Progressive disease developed but the lesions were smaller than those of the untreated animals. Ten rabbits were treated with dihydrostreptomycin (60 mg. daily for twenty days and then 30 mg. daily until the end of the experiment). Four of the animals developed progressive disease of the same type but it was less extensive than in the controls. Eleven rabbits received both corticotropin and dihydrostreptomycin in the doses recorded above. Two animals were sacrificed on the fourth day of the experiment. At the end of the experiment 2 had small scarred areas in the lungs, and 7 had normal lungs.

These experiments indicate that corticotropin does not materially reduce the resistance of previously sensitized rabbits to tuberculosis and that it can be administered with safety if dihydrostreptomycin is given simultaneously.

SUMARIO

El Efecto de la Corticotropina (HACT), la Dihidroestreptomicina y la Corticotropina y la Dihidroestreptomicina sobre la Tuberculosis Bovina Experimental del Conejo

Sesenta y seis conejos fueron sensibilizados con la inyección subcutánea de la cepa avirulenta R1v del *Mycobacterium tuberculosis*, después de lo cual se les infectó intratraquealmente con 0.25 ml. de la cepa Ravenel del bacilo tuberculoso bovino. Todos los 12 animales que sirvieron de testigos no tratados, manifestaron extensa tuberculosis evolutiva. Diez animales recibieron corticotropina (HACT), comenzando con una dosis inicial de 2.5 mg. cada seis horas. A plazos sucesivos de diez días, se rebajó la dosis en 2.5 mg. cada doce horas y en 2.5 mg. cada veinticuatro horas hasta el trigésimo día, desde cuya fecha se continuó con 1.25 mg. cada veinticuatro horas durante el resto del experimento. Se manifestó enfermedad evolutiva, pero las lesiones fueron más pequeñas que las observadas en los animales no tratados. A 10 conejos se les trató con dihidroestreptomicina (60 mg. diarios durante veinte días y luego 30 mg. diarios hasta el final del experimento). Cuatro de estos animales manifestaron enfermedad evolutiva del mismo tipo que la de los testigos, pero menos difusa. Once animales recibieron tanto corticotropina (HACT) como dihidroestreptomicina a las dosis mencionadas. Dos fueron sacrificados al cuarto día del experimento; al terminar el experimento 2 mostraban pequeñas zonas cicatrizadas en los pulmones, y 7 tenían pulmones normales.

Indican esos experimentos que HACT no reduce mayor cosa la resistencia de los animales previamente sensibilizados a la tuberculosis y que puede administrarse sin temor, si se da dihidroestreptomicina simultáneamente.

RESUME

L'effet de l'adréno-corticotrophine (ACTH), de la dihydrostreptomycine, de l'adréno-corticotrophine et de la dihydrostreptomycine sur la tuberculose bovine expérimentale chez le lapin

Soixante-six lapins ont été sensibilisés par l'injection sous-cutanée d'une souche avirulente de *Mycobacterium tuberculosis* Rlv, après quoi ils ont été inoculés par voie intra-trachéale avec 0,25 ml. de la souche Ravenel du bacille tuberculeux bovin. La totalité des douze animaux témoins non traités a présenté une tuberculose évolutive extensive. Dix animaux ont reçu l'hormone corticotrope (ACTH), en commençant par une dose initiale de 2,5 mg. toutes les six heures; à chaque période successive de dix jours, la dose a été réduite; 2,5 mg. toutes les 12 heures, puis 2,5 mg. toutes les 24 heures jusqu'au trentième jour et enfin 1,25 mg. toutes les 24 heures jusqu'à la fin de l'expérimentation. L'affection s'est progressivement développée, mais les lésions étaient plus réduites que chez les animaux non traités. Dix lapins ont été traités par la streptomycine (60 mg. par jour, pendant vingt jours, et ensuite 30 mg. par jour jusqu'à la fin de l'expérimentation). Quatre de ces animaux ont présenté des lésions évolutives du même type, mais moins extensives que chez les témoins. Onze lapins ont reçu à la fois l'hormone corticotrope (ACTH) et la dihydrostreptomycine aux doses indiquées ci-dessus. Deux animaux ont été sacrifiés au quatrième jour de l'expérimentation; a la fin de l'experimentation, deux animaux présentaient de petites aires de cicatrisation au niveau des poumons et sept avaient des poumons normaux.

Ces études expérimentales indiquent que l'ACTH ne réduit pratiquement pas la résistance des lapins antérieurement sensibilisés à la tuberculose et aussi que cette hormone peut être administrée avec sécurité si la dihydrostreptomycine est donnée en même temps.

REFERENCES

(1) Long, J. B., and Favour, C. B.: The ability of ACTH and cortisone to alter delayed type bacterial hypersensitivity, Bull. Johns Hopkins Hosp., 1950, *87*, 186.

(2) Tompsett, R., LeMaistre, C., Muschenheim, C., and McDermott, W.: Effects of ACTH on tuberculosis in humans, J. Clin. Investigation, 1950, *29*, 849.

(3) LeMaistre, C., Tompsett, R., Muschenheim, C., Moore, J. A., and McDermott, W.: Effects of adrenocorticotropic hormone and cortisone in patients with tuberculosis, J. Clin. Investigation, 1950, *30*, 445.

(4) Muschenheim, C.: The clinical effects of ACTH and cortisone in tuberculosis, Nat. Tubere. A. Tr., 1951, p. 69.

(5) Harris, S., and Harris, T. N.: Effect of cortisone on some reactions of hypersensitivity in laboratory animals, Proc. Soc. Exper. Biol. & Med., 1950, *74*, 186.

(6) Carlisle, J. M., Gibson, A., and Schmatolla, E.: Cortisone, Postgrad. Med., 1950, *8*, 113.

(7) Lurie, M. B., Zappasodi, P., Dannenberg, A. M., Jr., and Swartz, I. B.: Constitutional factors in resistance to infection: The effect of cortisone on the pathogenesis of tuberculosis, Science, 1951, *113*, 234.

(8) Hart, P. D'A., and Ress, R. J. W.: Enhancing effect of cortisone on tuberculosis in the mouse, Lancet, 1950, *2*, 391.

(9) Michael, M., Jr., Cummings, M. M., and Bloom, W. L.: Course of experimental tuberculosis in the albino rat as influenced by cortisone, Proc. Soc. Exper. Biol. & Med., 1950, *75*, 613.

(10) Cummings, M. M., Hudgins, R. C., Whorton, M. C., and Sheldon, W. H.: The influence of cortisone and streptomycin on experimental tuberculosis in the albino rat, Am. Rev. Tubere., 1952, *65*, 596.

(11) Spain, D. M., and Molomut, N.: Effects of cortisone on the development of tuberculous lesions in guinea pigs and on their modification by streptomycin therapy, Am. Rev. Tubere., 1950, *62*, 337.

(12) American Trudeau Society: The effect of cortisone and/or corticotropin on experimental tuberculous infections of animals, Am. Rev. Tuberc., 1952, *66*, 257.

(13) King, E. Q., Johnson, J. B., Batten, G. S., and Henry, W. L.: Report of a case of rapidly progressive pulmonary tuberculosis following cortisone therapy for rheumatoid arthritis, J.A.M.A., 1951, *147*, 238.

(14) Popp, C. G., Ottosen, P., and Brasher, C. A.: Cortisone and pulmonary tuberculosis, J.A.M.A., 1951, *147*, 240.

(15) Fred, L., Levine, M. H., Rivo, S. B., and Barrett, T. F.: Development of active tuberculosis during ACTH and cortisone therapy, J.A.M.A., 1951, *147*, 242.

(16) Traut, E. F., and Ellman, J.: Exacerbation of tuberculosis during treatment with cortisone, J.A.M.A., 1952, *149*, 1214.

(17) American Trudeau Society: The effect of cortisone and/or corticotropin on tuberculous infection in man, Am. Rev. Tuberc., 1952, *66*, 254.

(18) Wallner, L., Thompson, J. R., and Lichtenstein, M. R.: Clinical and histopathologic study of the effect of cortisone and corticotropin on tuberculosis, Am. Rev. Tuberc., 1952, *66*, 161.

(19) Kilbourne, E. D., and Horsfall, F. L., Jr.: Lethal infection with Coxsackie virus of adult mice given cortisone, Proc. Soc. Exper. Biol. & Med., 1951, *77*, 130.

(20) Shwartzman, G.: Poliomyelitis infection in cortisone treated hamsters induced by the intraperitoneal route, Proc. Soc. Exper. Biol. & Med., 1952, *79*, 572.

(21) Kass, E. H., Ingbar, S. H., Lundgren, M. M., and Finland, M.: The effect of ACTH and cortisone in pneumococcal and influenza viral infections in white mice, J. Lab. & Clin. Med., 1951, *31*, 750.

(22) LeMaistre, C., and Tompsett, R.: The evolution of tuberculous lesions in the guinea pig during administration of adrenocorticotropic hormone (ACTH) or cortisone, Am. Rev. Tuberc., 1952, *64*, 295.

(23) Lemaistre, C., and Tompsett, R.: The emergence of pseudotuberculosis in rats given cortisone, J. Exper. Med., 1952, *95*, 393.

(24) Bunn, P., and Drobeck, B.: Use of rabbit eye as a tissue to study tuberculosis: Effect of adrenal hormones upon course of disease and upon certain immunologic responses, Am. Rev. Tuberc., 1952, *66*, 175.

(25) Reinmuth, O. M., and Smith, D. T.: The effect of ACTH on pneumonia induced with tuberculin in the lungs of sensitized rabbits, Am. Rev. Tuberc., 1951, *64*, 508.

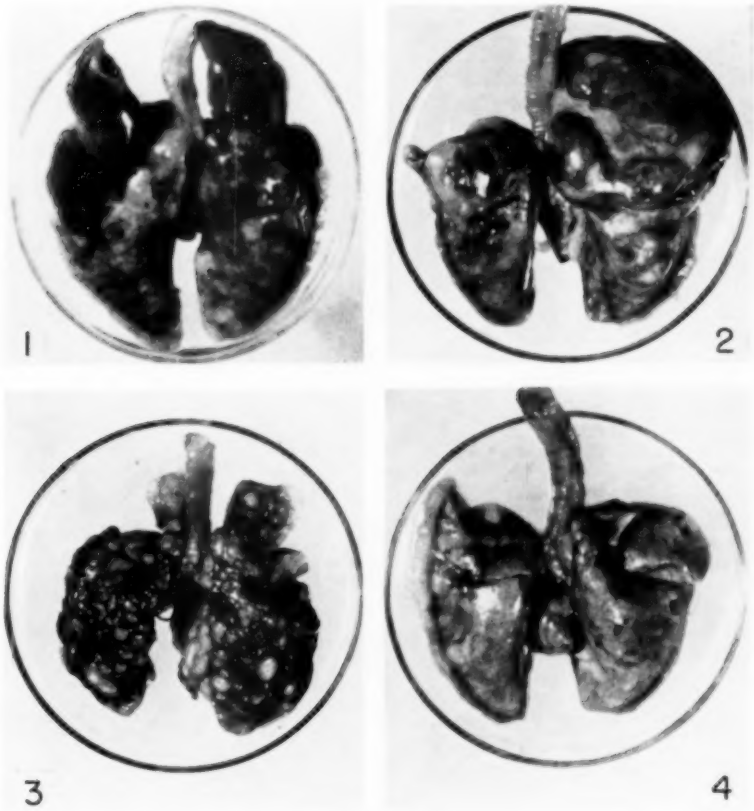


PLATE 1

FIG. 1. Photograph of lungs from untreated control rabbit, showing extensive fibrocaseous tuberculosis in all lobes. Animal died on ninety-ninth day of the experiment.

FIG. 2. Photograph of lungs from rabbit treated with dihydrostreptomycin for 120 days. The disease is most extensive in the right upper lobe. Animal sacrificed after 120 days.

FIG. 3. Photograph of lungs from rabbit treated with corticotropin for 120 days. The lungs are smaller than normal and infiltrated with small nodular lesions. Animal sacrificed after 120 days.

FIG. 4. Photograph of lungs from rabbit treated with corticotropin and dihydrostreptomycin for 120 days. The lungs are normal in size. There is a small depressed scarred area in the right upper lobe. The discolored spots in the left lung were apparently areas of atelectasis and not disease. Animal sacrificed after 120 days.

PLATE II

FIG. 1. Photograph of microscopic section of lungs from animal shown in plate I, figure 3 which was treated with corticotropin for 120 days. Note the discrete lesions and absence of collateral inflammation. H and E stain. Normal size.

FIG. 2. Photograph of microscopic section of lungs from animal shown in plate I, figure 4 which was treated with corticotropin and dihydrostreptomycin for 120 days. Note the residual scarring subjacent to the base of the section. H and E stain. Normal size.

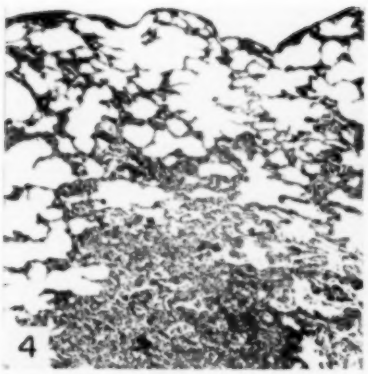
FIG. 3. Photograph of microscopic section of lungs from animal shown in plate I, figure 1 which remained untreated and served as a control. Note extensive fibrocaseous confluent tuberculosis. H and E stain. Normal size.

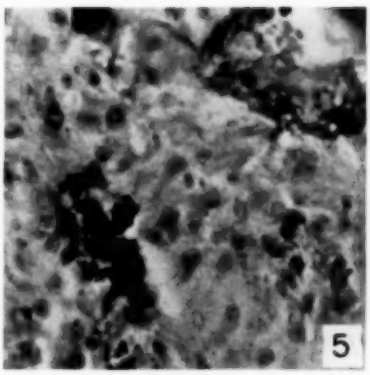
FIG. 4. Photograph of microscopic section of an area from plate I, figure 3. Note absence of caseation and fibroblastic proliferation. H and E stain. (× 60)

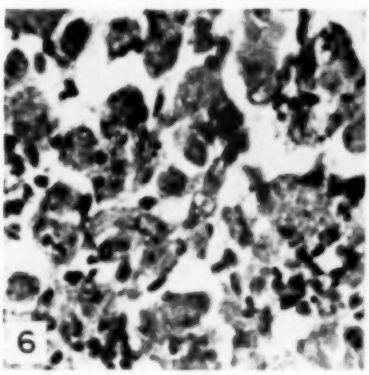
FIG. 5. Photograph of microscopic area of a nodule from plate I, figure 3. Note large mononuclear cells filled with tubercle bacilli. Carbolfuchsin and methylene blue stain. (× 600)

FIG. 6. Photograph of microscopic area from plate I, figure 4. Note large vacuolated mononuclear cells without tubercle bacilli and absence of caseation and fibroblasts. Carbolfuchsin and methylene blue stain. (× 600)

FIG. 7. Photograph of microscopic area from plate I, figure 1. Note giant cell and fibroblastic proliferation. Carbolfuchsin and methylene blue stain. (× 600)







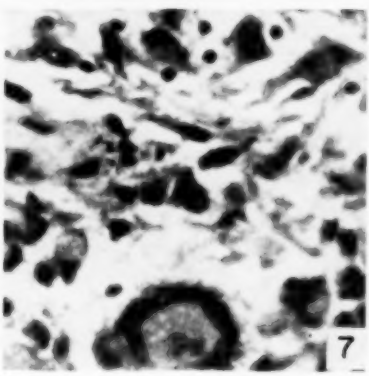


PLATE II

WITHDRAWAL SYMPTOMS UPON DISCONTINUANCE OF IPRONIAZID AND ISONIAZID THERAPY[1]

IRVING J. SELIKOFF, EDWARD H. ROBITZEK, AND GEORGE G. ORNSTEIN

(Received for publication November 18, 1952)

INTRODUCTION

The first published reports on the utilization of the hydrazine derivatives of isonicotinic acid (iproniazid and isoniazid) in the treatment of human tuberculosis (1–3) indicated that significant side effects might be observed in patients under such treatment. Although such side effects rarely included parenchymatous organ damage, central nervous system and autonomic nervous system symptoms were not infrequently observed, particularly with iproniazid (4). These symptoms included euphoria, nervousness, involuntary muscle twitching, hyperreflexia, and mild clonus, as well as dryness of the mouth, occasional difficulty in visual accommodation, infrequent difficulty in initiating micturition, constipation, headache, and evanescent vertigo. Peripheral neuropathy has also been seen occasionally. Dyspnea has been noted but its origin is obscure. Infrequently, with therapeutic dosage, but more often with high doses or in persons with inadequate renal function, somnolence and even coma have been observed. This vulnerability of the nervous system to large doses is suggested by pharmacologic studies (5), and the neurotoxic manifestations may be prevented or ameliorated by barbiturate sedation (6). Species differences have been recorded (7). In humans, such neurologic side effects have been more frequently observed in the aged, in the presence of severe anemia, in renal or hepatic insufficiency, and in patients with convulsive tendency or previous history of unstable personality. Adrenergic drugs and possibly general anesthesia appear to aggravate several of these symptoms, whereas barbiturates and prostigmine provide beneficial effects. Simultaneous therapy with other antituberculous agents (streptomycin) failed to alter the incidence or quality of these side effects (8).

The mechanism and pharmacology of such central and autonomic nervous system side effects is still undetermined. The writers were fortunate in obtaining a careful neuropathologic study during the post-mortem examination of one patient who died while under high iproniazid dosage therapy. These studies revealed no anatomic abnormality (9). The electroencephalographic studies which have been reported (10) revealed no abnormal patterns or any change from pretherapy electroencephalograms. However, most such encephalographic studies have been made with patients under isoniazid therapy. Nevertheless, the clinical pharmacologic observations leave little doubt of a direct effect upon both central and peripheral nervous tissue.

OBSERVATIONS

Recently, the present writers have studied, during a six-week period of drug discontinuance, a group of 65 patients who had been under therapy with iproniа-

[1] From the Department of Medicine, Sea View Hospital, New York, New York.

zid or isoniazid for sixteen to forty-four weeks. In this group, there were noted significant central nervous system side effects secondary to such discontinuance of therapy. The daily dosage received by these patients was 4 mg. per kg. of body weight in three daily divided doses with iproniazid, and 4 to 10 mg. per kg. of body weight with isoniazid.

In the 65 patients under study, 41 showed some reaction upon withdrawal of therapy. The incidence was considerably higher and the severity of the reaction considerably greater with iproniazid than with isoniazid. Of 56 patients previously treated with iproniazid, 39 (69.8 per cent) showed some reaction; while of 9 patients, each treated for twenty weeks with isoniazid, 2 showed mild reaction.

TABLE 1

INCIDENCE OF UNTOWARD SYMPTOMS FOLLOWING SUDDEN DISCONTINUANCE OF PROLONGED ISONIAZID AND IPRONIAZID THERAPY

	IPRONIAZID	ISONIAZID
Total cases	56	9
Withdrawal symptoms	39	2
Headaches	16	2
Insomnia	3	0
Dizziness	5	0
Unusual and excessive dreaming	20	0
Irritability and nervousness	15	0
Somnolence	2	0
Jumping legs	3	0
Duration of withdrawal symptoms		
Less than 2 weeks	23	0
2 to 4 weeks	12	2
4 to 6 weeks	4	0

Symptoms noted following withdrawal of drug therapy included headache, insomnia, vertigo, exaggerated dreaming and "nightmares," nervousness, depression, irritability, increased hyperreflexia and (in isolated individuals) drowsiness, diarrhea, weakness, and pruritis. These symptoms were noted in one or more patients following iproniazid therapy. The 2 patients previously treated with isoniazid complained only of headache. The headaches were usually moderate in intensity but were occasionally severe. They tended to be continuous, often appearing soon after withdrawal. The nightmares occurred in patients who had never been accustomed to such episodes and the information was usually volunteered within the first week of withdrawal. The incidence of the various types of reactions is outlined in table 1.

The onset of withdrawal symptoms was usually twenty-four to forty-eight hours after discontinuance of therapy. Occasionally it did not appear until the end of the first week. Symptoms continued with gradually decreasing intensity for periods up to six weeks, although they usually abated markedly in one week and were often gone in two. Both isoniazid patients had headaches intermittently

for a period of almost four weeks while, in the 39 patients treated with iproniazid, symptoms disappeared within two weeks in 23 cases. In 12 patients, symptoms persisted for almost four weeks; while in 4, almost six weeks elapsed before withdrawal symptoms disappeared. It seemed that symptoms occurred more frequently and with greater intensity in male than in female patients. Qualitatively the symptoms were the same in each sex.

Observations in other patients not included in the present study indicate that shorter periods of therapy, e.g., less than six weeks, are not followed by withdrawal symptoms. Moreover, therapy has been discontinued in a more gradual manner (during a seven- to ten-day period) in small groups of patients who had received both isoniazid and iproniazid therapy. In these circumstances, it was found that the withdrawal syndrome is altered but not eliminated. In these patients, withdrawal symptoms were delayed for approximately a week. When symptoms did occur, however, they were qualitatively similar although seemingly less intense than with abrupt discontinuance of chemotherapy. Further experiences with discontinuance over periods of three to four weeks have prevented withdrawal symptoms in another small group of patients.

The intensity of the symptoms did not require therapy in most cases. Barbiturate sedation is now utilized with fairly satisfactory control. In one case a dose of iproniazid was administered to a patient with severe headache, with relief of the headache within one hour but with its return several hours later. In another instance, prostigmine resulted in rapid relief of headache, followed by refreshing sleep. In this patient, symptoms of allergic rhinitis, relieved coincident with iproniazid therapy, returned within ten days upon discontinuance of therapy.

SUMMARY

A definite pattern of withdrawal has been observed following discontinuance of isoniazid and iproniazid therapy. The symptoms originated in the central nervous system and consisted mainly of headache, exaggerated dreams and nightmares, vertigo, nervousness, hyperreflexia, insomnia, irritability, and depression.

These symptoms appeared in approximately two-thirds of the patients previously treated with iproniazid, but in fewer instances and with much less intensity following withdrawal of isoniazid therapy.

The symptoms appeared within twenty-four to forty-eight hours following discontinuance of therapy, if this were abruptly done, and continued for periods ranging up to six weeks. More gradual withdrawal of the drugs delayed the onset of withdrawal symptoms but did not invariably abolish them. In most instances, the symptoms noted were mild and transitory but occasionally they caused considerable discomfort. In one instance, iproniazid gave temporary relief from headache, and prostigmine had more prolonged but similar beneficial effect. The symptoms encountered occurred only after prolonged hydrazide therapy. Other observations suggest that they do not commonly occur following short-term hydrazide therapy. One group of patients who received combined hydrazide-streptomycin therapy, which was discontinued following successful therapeutic

results, showed no variation from the above-noted phenomena upon withdrawal of the chemotherapy. It is concluded, therefore, that discontinuance of hydrazide therapy should be a gradual process whenever possible.

SUMARIO

Síntomas de Supresión al Discontinuar el Tratamiento con Iproniazid e Isoniazid

A continuación del abandono de la terapéutica con isoniazid e iproniazid, se ha observado un patrón bien definido de supresión. Los síntomas tenían su origen en el sistema nervioso central, consistiendo principalmente en cefalalgia, sueños y pesadillas exagerados, vértigo, nerviosidad, hiperreflexia, insomnio, irritabilidad y abatimiento.

Esos síntomas aparecieron en unas dos terceras partes de los enfermos tratados con iproniazid, pero en menos casos y en forma mucho menos intensa después de suspenderse la isoniazidoterapia.

Los síntomas aparecieron en término de veinticuatro a cuarenta y ocho horas de discontinuarse la terapéutica, si se hacía esto bruscamente, y continuaron durante períodos de tiempo, que llegaron hasta seis semanas. La supresión más gradual de las drogas demoró la iniciación de los síntomas de supresión, pero no los abolió invariablemente. En la mayor parte de los casos, los síntomas observados fueron leves y pasajeros, pero de vez en cuando ocasionaron mucha incomodidad. En un caso, el iproniazid suministró alivio temporal de la cefalalgia y la prostigmina ejerció efecto beneficioso similar, pero más prolongado. Los síntomas observados sólo se presentaron tras una hidracidoterapia prolongada. Otras observaciones sugieren que no ocurren habitualmente después de la hidracidoterapia usada por poco tiempo. Un grupo de enfermos que recibió hidracido-estreptomicinoterapia combinada, que se discontinuó al obtenerse favorables resultados terapéuticos, no reveló variación de los fenómenos mencionados al suspenderse la quimioterapia. Dedúcese, pues, que el abandono de la hidracidoterapia debe ser gradual, siempre que sea posible.

RESUME

Symptômes de suppression survenant à l'arrêt de la thérapie par l'Iproniazide et l'Isoniazide

Des symptômes de suppression d'un type particulier o ont été observés à la suite de l'interruption du traitement par l'isoniazide et l'iproniazide. Les symptômes avaient leur origine dans le système nerveux central et consistaient principalement en: céphalée, exagération du rêve et du cauchemar, vertige, nervosité, exagération des réflexes, insomnie, irritabilité et dépression.

Ces symptômes se sont manifestés chez environ deux tiers des malades traités précédemment par l'iproniazide, mais, après l'arrêt de la thérapie par l'isoniazide, ils sont apparus moins souvent et avec moins d'intensité.

Les symptômes se sont manifestés vingt-quatre à quarante-huit heures après l'arrêt du traitement, quand cet arrêt avait été brutal, et ils se prolongeaient pendant des périodes pouvant atteindre six semaines. Une interruption plus graduelle de la médication retardait l'apparition des symptômes de suppression, mais ne les abolissait pas toujours. Dans la plupart des cas, les symptômes observés étaient légers et transitoires, mais parfois les malaises étaient sévères. Dans un cas, l'iproniazide a déterminé une amélioration temporaire des maux de tête; la prostigmine avait produit un effet plus prolongé, mais également favorable. Les symptômes observés ne se sont produits qu'après un traitement prolongé par l'hydrazide. Les autres observations suggèrent que ces symptômes sont habituellement peu fréquents à la suite d'un traitement de courte durée par l'hydrazide. Dans un groupe de malades ayant reçu un traitement où l'hydrazide et la streptomycine étaient associées, l'arrêt de la médication, qui avait donné de bons résultats, n'a permis d'observer aucune variation dans les phénomènes décrits ci-dessus quand la chimiothérapie a été supprimée. En conséquence, les auteurs concluent que l'arrêt de la thérapie par l'hydrazide doit se faire par degré quand cela est possible.

REFERENCES

(1) Robitzek, E. H., Selikoff, I. J., and Ornstein, G. G.: Chemotherapy of human tuberculosis with hydrazine derivatives of isonicotinic acid, Quart. Bull., Sea View Hosp., 1952, *13*, 27.

(2) Selikoff, I. J., and Robitzek, E. H.: Tuberculosis chemotherapy with hydrazine derivatives of isonicotinic acid, Dis. of Chest, 1952, *21*, 385.

(3) Robitzek, E. H., and Selikoff, I. J.: Hydrazine derivatives of isonicotinic acid (Rimifon, Marsilid) in the treatment of active, progressive caseous-pneumonic tuberculosis: A preliminary report, Am. Rev. Tubere., 1952, *65*, 402.

(4) Selikoff, I. J., Robitzek, W. H., and Ornstein, G. G.: Toxicity of hydrazine derivatives of isonicotinic acid in the chemotherapy of human tuberculosis, Quart. Bull., Sea View Hosp., 1952, *13*, 17.

(5) Rubin, B., Hassert, G. L., Jr., Thomas, B. G. H., and Burke, J. C.: Pharmacology of isonicotinic acid hydrazide (Nydrazid), Am. Rev. Tubere., 1952, *65*, 392.

(6) P'an, S. Y., Markaroglu, L., and Reilly, J.: The effects of barbiturates on the toxicity of isoniazid (isonicotinic acid hydrazide), Am. Rev. Tubere., 1952, *66*, 100.

(7) Lewis, R. A.: Tolerance of man for isonicotinylhydrazines, Antibiotics, 1952, *2*, 285.

(8) Robitzek, E. H., Selikoff, I. J., Bloch, W., and Mamlok, E.: Combined therapy of pulmonary tuberculosis with hydrazines of isonicotinic acid and dihydrostreptomycin, Quart. Bull. Sea View Hosp., 1952, *13*, 171.

(9) Gold, G.: In preparation.

(10) Quarterly Progress Report of the Veterans Administration Army-Navy Study of the Chemotherapy of Tuberculosis, July, 1952, pp. 31–32.

LETHAL AND CYTOLOGIC EFFECTS OF LYSOZYME ON TUBERCLE BACILLI[1,2]

QUENTIN N. MYRVIK,[3] RUSSELL S. WEISER, AND HILDA D. AGAR

(Received for publication August 13, 1952)

INTRODUCTION

In a previous communication Myrvik and Weiser (1) reported that a tuberculostatic[4] substance with lysozyme-like properties is present in the serum of rabbits immunized with heat-killed tubercle bacilli in Freund's adjuvants (mineral oil and Falba).[5] Since preliminary trials indicated that the minimum concentrations of the lysozyme-like serum substance and crystalline egg-white lysozyme necessary to inhibit growth of tubercle bacilli do not possess measurable bactericidal activity, it appeared desirable to determine whether higher concentrations of these substances might exert cytologic and lethal effects.

Corper (2) conducted investigations on the possible role of lysozyme in resistance to tuberculosis. He did not succeed in his attempt to demonstrate *in vitro* tuberculostatic or tuberculocidal effects with neutral saline extracts of the acetone dried organs of guinea pigs.[6] Apparently the lysozyme content of the extracts was not determined. To the present writers' knowledge, the only published report on the effect of lysozyme on tubercle bacilli in which known preparations of high activity were used is that of Wolff (3), who observed that, when tubercle bacilli were suspended in "lysozyme concentrates" prepared from fresh egg white and digested for one hour, the material failed to produce growth when cultured on Dorset's egg medium. It is possible that the lysozyme carried with the inoculum to the culture medium was bacteriostatic and that no bactericidal action actually took place during digestion.

Review of Literature

Despite the paucity of investigations on the effects of known lysozyme preparations on tubercle bacilli, there are a number of published studies on the tuberculostatic and tuberculocidal action of blood, serum, tissues, and tissue extracts in which the activity reported was probably due to lysozyme.

[1] From the Department of Microbiology, University of Washington School of Medicine, Seattle, Washington.

[2] This work has been supported (in part) by the State of Washington Funds for Medical and Biological Research, and (in part) by the Alice McDermott Research Foundation of the University of Washington.

[3] Medical Research Fellow, National Tuberculosis Association. Present address: Department of Microbiology, University of Virginia School of Medicine, Charlottesville, Virginia.

[4] The term *tuberculostatic* is used to indicate bacteriostasis for the tubercle bacillus.

[5] The mineral oil used was Bayol F, obtained from Stanco Distributors, Inc., 216 West 14 Street, New York, New York; and the Falba, from Pfaltz and Bauer, Inc., Empire State Building, New York, New York.

[6] The term *tuberculocidal* is used to indicate bactericidal action on the tubercle bacillus.

The lysozyme-like nature of the active principle in the various materials tested is indicated in many of the studies cited below by the following properties:

> It is present in low concentrations, the concentration varies markedly among species and among individuals of the same species, the principle is heat stable, the principle is more active against *M. phlei* than against *M. tuberculosis*, and, finally, in the case of serum, no other tuberculo-inhibitory substance has been described to date. It should be emphasized, however, that the literature cited does not contain convincing proof that the active principle involved was lysozyme.

As early as 1904, Baldwin (4) presented highly suggestive evidence that the serum of calves vaccinated with *Mycobacterium tuberculosis* var. *hominis* is inhibitory for tubercle bacilli. The principal early investigation on the tuberculocidal action of tissue fluids and extracts was reported by Kling (5), who observed that extracts obtained from the neutrophils of guinea pigs, cats, and rabbits are bactericidal for *M. tuberculosis* var. *hominis*. Kling also demonstrated that a pronounced decline in the viability of saprophytic acid-fast bacteria occurs when the organisms are incubated in animal sera.

Kirchner (6) was unable to detect any bactericidal property in the sera of tuberculous humans tested against virulent tubercle bacilli. More recently, Hanks and Evans (7) have reviewed much of the earlier literature on the subject and in their own careful and extensive investigations failed to detect any appreciable tuberculocidal power of plasma, serum, or serum-leukocyte mixtures derived from the blood of normal or immunized animals. They were also unable to demonstrate that there is any relationship between the resistance of given animal species to avian, bovine, or human tubercle bacilli and the decline in the viability of the respective organisms after being suspended for many hours in the blood of the species. It is of interest that with *M. phlei* they did observe a ". . . definitely measurable reduction in colony count . . ." after twenty-four to ninety-six hours of treatment with either the blood or serum of rabbits. This effect was not attributable to the influence of antibody, complement, or phagocytosis and was thought to be due to the lack of suitable nutrients in the serum rather than the presence of any bactericidal substance. In light of present knowledge, however, the observation of Hanks and Evans that not all rabbit sera were active and that active sera were not materially affected by heating at 56° C. makes it seem probable that the activity of the sera used was due to lysozyme (1).

A similar decline in the viability of *M. phlei* suspended in various animal sera was noted by Kling (5) and by Hedvall (8). Indeed, the latter writer expressed the view that this inhibitory property of serum is due to "beta-lysins" since temperatures of 70° C. were necessary to destroy the activity.

Martenstein (9) was among the first to report that sera of patients with sarcoidosis and certain types of tuberculosis possess a remarkable inhibitory effect on tubercle bacilli. Kallos and Nathan (10) confirmed the investigations of Martenstein and, in addition, noted that sera from patients with combined pulmonary and skin tuberculosis suppress the growth of virulent strains of tubercle bacilli *in vitro* more strongly than sera from normal persons or patients with only the pulmonary form of the disease. They also made the very interesting observation that the sera of these same patients with skin tuberculosis do not inhibit cultures of tubercle bacilli isolated from the infected skin areas of the patients. Since it is well established that tubercle bacilli isolated from the lesions of skin tuberculosis are usually of low virulence (11), the question arises whether high virulence is incompatible with lysozyme resistance.

Pagel (12, 13) has recently confirmed and greatly extended the work of Kallos and Nathan. He noted that inhibiting sera are regularly found in the special form of chronic

pulmonary tuberculosis termed "hematogenous" or chronic miliary tuberculosis and, moreover, that the sera from patients with generalized and disseminated types of tuberculosis do not possess appreciable inhibitory power for tubercle bacilli. As a result of these findings, Pagel proposed that the growth-preventive power of the serum does not rest upon the clinical severity or extent of the tuberculosis but rather upon the type of tuberculous development. He noted that "bactericidal" sera are not confined to cases of skin tuberculosis but are also a feature of the universal complex of chronic hematogenous tuberculosis of the lung.

Courmont and Gardere (14–17) also studied the tuberculostatic effect of sera from tuberculous subjects. They found that among tuberculous patients a good correlation exists between the high "bactericidal" activity of sera and favorable prognoses. These writers proposed that the "bactericidal" power of serum reflects the individual's resistance to tuberculosis. Results similar to those of the above authors were obtained by Rist and Ionescu (18), who determined the antibacterial properties of pleural effusions from tuberculous patients for tubercle bacilli by culturing mixtures of the pleural effusion and bacilli after two to thirty-six hours of incubation. The reports on the tuberculo-inhibitory action of tuberculous sera are in general agreement with the reports of the inhibition of tubercle bacilli by whole blood and plasma made by Bannerman (19), Meissner (20), Sonak (21), and Wright (22). Lurie (23, 24) has made the highly important observation that body fluids of immunized rabbits and guinea pigs exert an *in vivo* tuberculostatic action. Although the basis of this tuberculostatic effect was unexplained at the time, it now appears possible that the inhibition he observed was due to lysozyme.

Mayama (25) has recently demonstrated that both whole blood and serum of lepers possess strong tuberculostatic activity. He has also shown that the whole blood of rats, which is normally not tuberculostatic, becomes strongly inhibitory following infection with the organism of rat leprosy. Mayama's review of the literature on the tuberculostatic activity of blood and serum includes references which, for lack of space, are not presented here.

Inasmuch as the composition of the cell surface apparently determines the virulence of microorganisms as well as their susceptibility to lysozyme (26), studies on the cytologic action of lysozyme on cells of varying lysozyme resistance and animal virulence assume great importance.

The chemical alterations responsible for the changes in bacterial cytology produced by lysozyme are not fully understood. It is generally considered that the primary effect is that of the depolymerizing action of lysozyme on an amino-carbohydrate substrate present in the bacterial cell wall (27) and possibly of carbohydrate linkages with nucleic acid or with protein (28). The lysis which then follows with certain of the susceptible bacteria is believed to take place as the result of the secondary action of autolytic enzymes of the cell (28).

In studies on the cytology of lysozyme-susceptible heat-killed *Staphylococci* and *Clostridium welchii* conducted with the ordinary light microscope, Webb (28) has shown that the organisms become gram-negative and liberate ribonucleic acid following treatment with lysozyme. He has suggested that the change in gram-staining behavior results from the cleavage of ribonucleic acid and carbohydrate linkages of the gram complex and linkages between the ribonucleic acid of the gram complex and cell protein. Apparently the major portion of this cell protein remains with the cell cyto-skeleton following lysozyme treatment. In an attempt to explain species variations in susceptibility to lysozyme Webb states:

It is, however, possible that two carbohydrates exist in *M. lysodeikticus*, both of which are susceptible to the action of lysozyme, the one forming part of the gram complex and the other being contained in the somatic portion of the cell. The fortuitous occurrence of a carbohydrate substance in the cell bodies of *M. lysodeikticus* capable of being more completely hydrolysed by lysozyme than the carbohydrate of the gram complex may in part explain the difference in susceptibility towards the enzyme which exists between *M. lysodeikticus* and most other organisms.

On the basis of stained preparations it has been reported that a marked swelling of the cell takes place prior to lysis (26, 29, 30). Fleming (29) studied living cells of *M. lysodeikticus* treated with tears. Swelling of the cells was noted in wet preparations with both darkfield illumination and transmitted light and, as well, by Burris' method of negative staining and ordinary bacterial stains. Under darkfield the cells were observed to first swell and then gradually disappear. During the process, minute granules became apparent. Boasson (31) has conducted darkfield and packed cell volume studies with phenol-killed *M. lysodeikticus* treated with lysozyme which indicate that the swelling reported by others may be an artifact due to reduced cell turgor and the resultant greater flattening in stained preparations. He expressed the view that the cell wall is not destroyed but becomes more permeable to the cellular contents. It is possible, of course, that phenol-killed cells behave differently toward lysozyme than living cells.

Georgi and associates (32) have noted in phase contrast studies that within a few minutes after treatment with lysozyme the cells of *Bacillus stearothermophilis* become invisible and liberate enzyme-rich "red fraction" granules which are swollen. The writers expressed the view that swelling of the granules is a consequence of their liberation from the cell into the surrounding medium and analogous to a similar swelling observed with the mitochondria of animal cells. The resistance of the free cell granules to further change by prolonged exposure to lysozyme was not studied.

Kern and associates (33) have recently employed the electron microscope to study the cytologic action of lysozyme. They have shown that lysozyme treatment of *M. lysodeikticus* causes swelling of the cell which apparently results in the rupture of the cell wall and dispersal of the cell contents. It was noted that the two cytoplasmic bodies normally found within the cell are not destroyed by lysozyme action. The final change was the destruction of the cell membrane. In contrast to the cytologic changes observed in *M. lysodeikticus*, these investigators found that the more highly resistant organism *Staphylococcus aureus* K_1 did not undergo rapid dissolution even with lysozyme concentrations of 3 mg. per ml. Instead, a slow dissolution of an "outer viscous" portion of the cell took place over a period of several hours, leaving the cell membrane and an inner dense cytoplasmic portion. They reported that the viable count of the treated suspensions of *S. aureus* K_1 continued to decrease to very low values, whereas the direct count by the Levy-Hausser method remained high.

MATERIALS AND METHODS

Strains of Mycobacteria employed: The BCG and Ravenel strains of *M. tuberculosis* var. *bovis* used in the present investigations possessed morphologic, cultural, and pathogenic properties generally considered to be typical of the strains.[7] The history of the origin of the avian strain was lacking. However, it was culturally typical. Its pathogenicity was not determined.

[7] The Ravenel strain of *M. tuberculosis* var. *bovis* was kindly provided by William Steenken, Jr., Trudeau Sanatorium, Trudeau, New York.

Preparation of bacterial suspension: The strains of *Mycobacteria* used in the present investigations were grown on Sauton's medium at pH 6.8 for six to eight days. The surface growth was ground in a sterile mortar and the ground cell mass was suspended in sterile saline containing 0.04 per cent of Tween 80.[8] The organisms were washed twice with saline-Tween and resuspended in a similar saline-Tween solution. The suspension was then centrifuged lightly to remove clumps of cells and the supernatant was diluted in saline-Tween to equal No. 1 McFarland barium sulfate standard (0.25 mg., wet weight, per ml.). This stock suspension was composed largely of single cells as observed in stained smears.

Preparation of the lysozyme solution: The form of crystalline egg-white lysozyme used for most of the work was the chloride.[9] In some specified instances the crystalline isoelectric form was employed. The isoelectric form was prepared in this laboratory from fresh egg white by the method of Alderton and Fevold (34). Stock solutions of lysozyme were prepared in sixtieth molar phosphate buffer, pH 6.8, and sterilized by filtration through a Swinney filter.

Lysozyme treatment of microorganisms for electron microscope study: Treatment was carried out in sets of screw-cap tubes. To each tube in the lysozyme set was added 1 ml. of Proskauer and Beck broth, 0.9 ml. of the stock bacterial suspension, and 0.1 ml. of the proper dilution of lysozyme.[10] A control set of tubes was similarly prepared except that 0.1 ml. of sixtieth molar phosphate buffer, pH 6.8, was substituted for the lysozyme. Measurements with a pH meter showed the final values to be identical in the two sets of tubes. The control and lysozyme sets of tubes were incubated for periods up to ninety-six hours at 37° C., and 0.1 ml. aliquots of the suspensions were removed at various time intervals for examination with the electron microscope. The aliquots were centrifuged, the supernatant was removed, and the organisms were resuspended in 0.5 ml. of distilled water. The suspension was placed in a sloped Petri dish and several amounts of each preparation were made by slowly sweeping the grids through the suspension. The excess fluid which adhered to the grids was quickly drawn off by capillary action with narrow strips of heavy blotting paper. This technique proved satisfactory since tubercle bacilli tend to float on the surface of small drops. When the pathogenic Ravenel strain of *M. tuberculosis* var. *bovis* was used, the grids were exposed to a 40-inch cold quartz mercury arc lamp at a distance of 18 inches for one hour to reduce the hazard of infection. In most instances, "formvar" films were used for unshadowed preparations and collodion films for those which were shadowed. The samples were shadowed with nickel at an angle of 15 degrees and photomicrographs were taken at a magnification of 7,000 with an RCA model EMU 2B electron microscope equipped with an unbiased gun.

Determination of the lethal effects of lysozyme: The stock suspension of the BCG strain of *M. tuberculosis* described above was diluted to equal a No. 2 McFarland barium sulfate standard (0.5 mg., wet weight, per ml.). The ratio of ingredients in the final suspension consisted of 0.5 ml. of Dubos broth (35), 0.4 ml. of the above stock bacterial suspension, and 0.1 ml. of the desired dilution of lysozyme. Control tubes were prepared which were identical in composition except that the lysozyme solution was replaced by a similar volume of physiologic saline containing sixtieth molar phosphate buffer pH 6.8. Incubation of the preparations was carried out at 37° C. and samples were removed at various time intervals for examination. Serial tenfold dilutions of the samples were prepared and fixation plates were poured with nutrient agar containing 2 per cent glycerol and 5 per cent sterile bovine serum. The plates were sealed with rubber electricians's tape, incubated for three or four weeks at 37° C., and colony counts were made. Stained smears were made of each sample prior to dilution and several hundred organisms were counted to determine the extent of

[8] Proprietary name of the polyoxyethylene derivative of Sorbitan monooleate, Atlas Powder Co., Wilmington, Delaware.

[9] The crystalline lysozyme chloride was generously supplied by Armour and Co., Chicago, Illinois.

[10] Unless otherwise specified, the term *lysozyme* is used hereafter to designate crystalline egg-white lysozyme chloride.

clumping since this is an important source of error in plate counts of suspensions of tubercle bacilli which are allowed to settle. In addition, there is a tendency for tubercle bacilli to clump in solutions of lysozyme.

RESULTS

Lethal Action of Egg-White Lysozyme Chloride on the BCG Strain of M. Tuberculosis

In the present experiments, the suspensions, even in the most concentrated lysozyme preparations with the longest incubation intervals, averaged 4 to 7 bacilli per clump compared with an average of 2 or 3 cells per clump at the beginning of incubation. The lysozyme-treated suspensions did not show clumps averaging more than 1 or 2 cells greater than the control suspensions. It was believed that the plate counts provided a significant measure of the lethal effects of lysozyme since the reduction in plate count observed was 99 per cent and was far greater than any possible error which might be due to clumping of the cells.

TABLE 1

THE LETHAL EFFECT OF 1,000 γ PER ML. OF LYSOZYME ON BCG

	INCUBATION INTERVAL, HOURS			
	0	3	24	48
Colony count of control suspension	5.9×10^6	6.0×10^6	6.2×10^6	6.1×10^6
Colony count of treated suspension	5.4×10^6	5.8×10^6	1.2×10^6	6.4×10^4
Per cent survival	"100"	"100"	19	1

TABLE 2

THE LETHAL EFFECT OF 2,000 γ PER ML. OF LYSOZYME ON BCG

	INCUBATION INTERVAL, HOURS		
	0	24	48
Colony count of control suspension	1.3×10^6	1.3×10^6	1.8×10^6
Colony count of treated suspension	1.4×10^6	1.3×10^5	3.6×10^4
Per cent survival	"100"	10	2

In the first trials on the lethal effects of lysozyme on BCG, the concentrations of lysozyme employed were 100 and 500 γ per ml. Plate counts were made of samples taken at zero, three, twenty-four, and forty-eight hours. These preliminary trials did not indicate that lysozyme in the concentrations used exerts any appreciable lethal effect on the organisms. The plate counts made of the control and lysozyme-treated organisms varied within a range of plus-minus 10 per cent.

A similar trial was then made using a final concentration of lysozyme of 1,000 γ per ml. This concentration of lysozyme resulted in a lethal effect on BCG which was pronounced at the twenty-four- and forty-eight-hour intervals. The results of the experiment are presented in table 1. The plate count at the forty-eight-hour interval showed that only 1 per cent of the organisms had survived the lysozyme treatment.

In order to determine whether a further increase in the concentration of lysozyme would accelerate the rate of killing, another experiment was conducted which employed a final concentration of lysozyme of 2,000 γ per ml. The results presented in table 2 show that 2,000 γ of lysozyme per ml. did not appreciably increase the killing over that previously observed with 1,000 γ per ml.

Both experiments demonstrate in a striking manner that lysozyme is lethal for tubercle bacilli when the concentration of lysozyme is high and the exposure intervals are sufficiently long.

Electron Microscope Observations of Tubercle Bacilli Treated with Lysozyme Chloride

Cytologic changes in the BCG strain of M. tuberculosis: It was found that 1,000 to 2,000 γ of lysozyme per ml. produced marked cytologic changes in organisms of the BCG strain, especially at incubation periods of forty-eight hours and longer. In contrast, 100 γ of lysozyme per ml. produced very little change and then only in a small percentage of the organisms even when the incubation interval was extended to ninety-six hours.

Examination of preparations made from samples taken at various intervals from suspensions treated with 1,000 to 2,000 γ per ml. showed that there is a progressive change in cytologic appearance of the organisms. At any of the time intervals (twenty-four, forty-eight, and seventy-two hours) studied, however, cells in all stages of change were present.

Shadowed pictures depicting the sequence of changes which resulted from treatment with 2,000 γ of lysozyme are shown in figure 1. Figure 1*A* shows untreated control cells of BCG. Figure 1*B* shows a cell in an early stage of change.

The increased diameter of the cell outline, which was readily discernible in magnifications of 56,000, may not represent true swelling but may, instead, be due to loss of turgor with consequent flattening of the cell membrane during the drying process, as claimed by Boasson (31). The most notable change is an apparent shrinkage and lobulation of the cytoplasm, accompanied by an increase in density to electrons and masking of the characteristic internal granules which are fully apparent in the control preparations. That the granules were still present in the treated preparation was evidenced by the fact that characteristic granule shadows were seen in other shadowed preparations. In figure 1*C* a terminal stage is shown in which only the irregular beaded "shafts" of protoplasm remain with no trace of the cell membrane.[1] In some of the other preparations examined, cells were seen in which the protoplasmic shafts were apparently in the act of breaking out of the partially collapsed cell walls. It was clearly evident that more cells were of the dense, beaded shaft variety at the forty-eight-hour incubation period than at the twenty-four-hour period. At the seventy-two-hour period essentially every cell had been converted to the beaded shaft form.

The normal control cells did not show any of the forms seen in treated prepa-

[1] The term *shaft* is arbitrarily used to designate the rod shaped mass which is thought to represent the remains of the entire contents of the cytoplasmic membrane.

FIG. 1. BCG strain of *M. tuberculosis* var. *bovis*. Magnification 7,000 ×; negative prints.
A. Untreated control
B. Treated with 2,000 γ of lysozyme per ml. for seventy-two hours
C. Treated with 2,000 γ of lysozyme per ml. for ninety-six hours

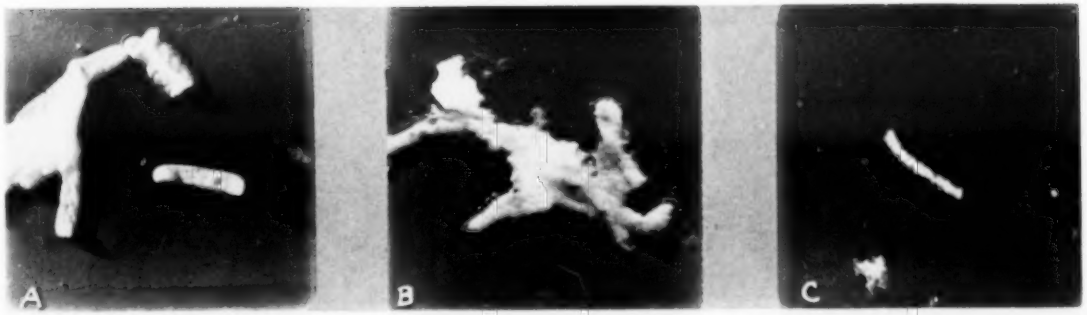


FIG. 2. Ravenel strain of *M. tuberculosis* var. *bovis*. Magnification 7,000 ×; negative prints.

A. Untreated control
B. Treated with 2,000 γ of lysozyme per ml. for seventy-two hours
C. Treated with 2,000 γ of lysozyme per ml. for seventy-two hours

rations. The increase in the degree of the cytologic change which occurred with increasing time of treatment paralleled the lethal effects observed in the previous experiments on the lethal action of lysozyme. Stains made of the preparations which showed only shaft forms and examined with the light microscope revealed them to be strongly acid-fast even though shrunken and irregular in outline.

Cytologic Changes in the Ravenel Strain of M. Tuberculosis var. Bovis

The highly pathogenic Ravenel strain of *M. tuberculosis* var. *bovis* was treated with 2,000 γ of lysozyme per ml. and examined with the electron microscope for cytologic changes.

The results obtained were similar to those seen when the BCG strain was treated with lysozyme. In figure 2 typical pictures may be seen which represent the sequence of cytologic changes observed when lysozyme was allowed to act on organisms of the Ravenel strain. In figure 2*A* a typical cell grouping of normal cells is shown, and figure 2*B* depicts cells in an early stage of change. By comparing the cells at the edge of the clumps, it can be seen that the protoplasm of the treated cells shows an increased density to electrons; a transformation similar to that previously recorded for BCG. In figure 2*C* the final stage of change is depicted in which the cell wall has apparently disintegrated, leaving behind the bare protoplasmic shaft.

Cytologic changes in M. tuberculosis avium: Since it was previously found that *M. tuberculosis avium* is not inhibited in its growth by 200 γ of lysozyme per ml. (1), it seemed desirable to subject this organism to higher concentrations of lysozyme to note whether cytologic changes can be produced.

The results of such a trial showed that *M. tuberculosis avium* is cytologically susceptible to 2,000 γ of lysozyme per ml. when incubation is carried out at 37°C. for forty-eight to seventy-two hours. The cytologic changes were similar to those observed with BCG cells and showed much the same intermediate stages as those presented for BCG in figure 1. Electron micrographs showing the effect of lysozyme on *M. tuberculosis avium* are presented in figure 3. Normal control cells of *M. tuberculosis avium* are shown in figure 3*A*, and lysozyme-treated cells in figure 3*B*.

The lysozyme-treated cells illustrated in figure 3*B* show one of the early cytoplasmic changes characteristic of lysozyme action on the cells of BCG, namely, an increased density to electrons. Although there is no apparent change in diameter of the cells, it is notable that many of them are longer than normal, which suggests that initial lysozyme action against these organisms may have blocked the ability to divide but not the ability to increase in length.

A more advanced stage of change in which protoplasmic shafts have formed is shown in figure 3*C*. The lobulation of the shafts is not as marked as that seen with BCG. The shafts illustrated are apparently still within the cell membranes. In contrast, the BCG cells similarly treated were noted to be largely free of their cell membranes. In figure 3*D* are shown cell membranes that have broken open and become flattened. Such membranes were seen in a few instances in the treated preparations but not in the controls. Although it is possible that remnants

of this appearance may not have resulted from lysozyme action, it seems significant that they were never observed in control preparations. It may be that the shafts have escaped from the cells, leaving only the membranes.

It was also evident that *M. tuberculosis avium* is cytologically much more resistant to lysozyme than the cells of BCG. With cells of the avian strain, cyto-

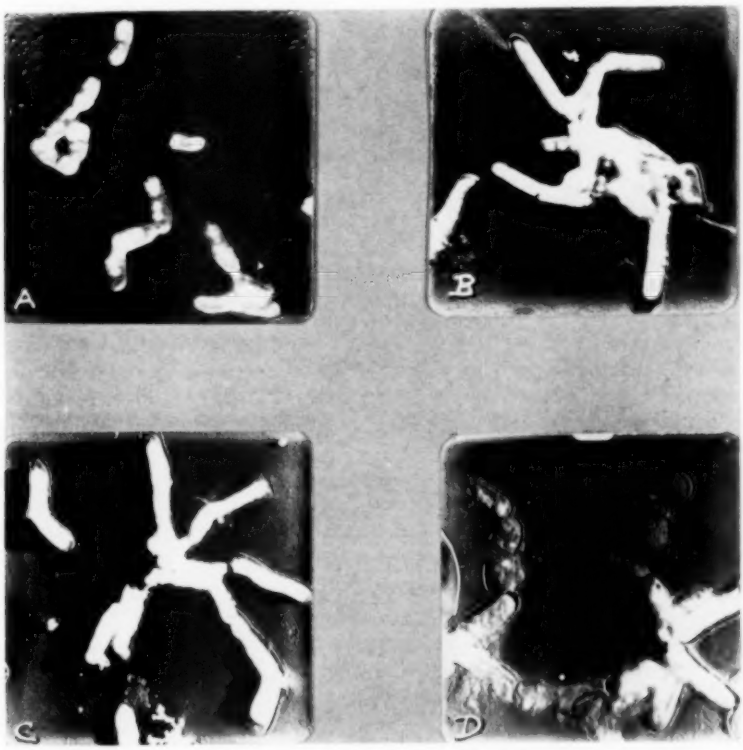


FIG. 3. *M. tuberculosis avium*. Magnification 7,000 ×; negative prints.
A. Untreated control.
B. Treated with 2,000 γ of lysozyme per ml. for forty-eight hours.
C. Treated with 2,000 γ of lysozyme per ml. for seventy-two hours.
D. Treated with 2,000 γ of lysozyme per ml. for seventy-two hours.

logic changes became apparent in a small percentage of cells after a treatment interval of forty-eight hours. Even after seventy-two hours of treatment, only approximately 50 per cent of the cells were converted to the shaft form. With cells of the BCG strain, the cytologic changes were evident in the majority of cells within forty-eight hours. After seventy-two hours, 95 per cent or more of the cells presented shaft forms.

Electron Microscope Observations of Mycobacteria Treated with the Isoelectric Form of Lysozyme

The experiments reported above with the cells of BCG were repeated with the isoelectric form of lysozyme. The cytologic changes were identical with those reported for lysozyme-chloride-treated cells.

Miscellaneous Observations

In addition to the work with young living cells of the BCG strain, cells killed by heat treatment at 100° C. for ten minutes were exposed to 2,000 γ of lysozyme per ml. for seventy-two hours and examined with the electron microscope. Preparations made from living untreated three-month-old cultures of the BCG strain were also examined. None of the cells in these preparations displayed any of the cytologic changes observed with young living cells treated with lysozyme.

DISCUSSION

The results presented above show that avian and mammalian tubercle bacilli treated with high concentrations of crystalline egg-white lysozyme for prolonged periods of time exhibit pronounced cytologic changes. With the BCG strain, the increase in the number of cells cytologically affected and the degree of cytologic change which occurred with increasing time of treatment paralleled the lethal effect.

From the description of the cytologic changes reported by Kern (33) with *Staphylococcus aureus* treated with 3,000 γ of lysozyme per ml., it appears that *M. tuberculosis* presents a similar pattern of cytologic and lethal effects.

The observation that heat-killed tubercle bacilli do not show cytologic changes detectable with the electron microscope parallels the findings of Fleming and Allison (36) with heat-killed *M. lysodeikticus* and supports the concept that the most readily observable cytologic changes are secondary to the action of lysozyme on its substrate and depend on autolytic enzymes of the cell.

The finding that the cytoplasmic shafts which are apparently free of cell membranes are strongly acid fast makes it seem probable that acid-fastness does not depend upon an intact cell membrane.

The insolubility of the "naked" cytoplasmic shafts suggests that they are rich in lipids, which is consistent with the high lipid content of tubercle bacilli.

The cell membranes of *M. tuberculosis avium* are apparently more resistant to lysozyme action than the cell membranes of *M. tuberculosis* var. *bovis*. It is notable that *M. tuberculosis avium* is also more resistant to the bacteriostatic effects of lysozyme than *M. tuberculosis* var. *bovis* (1).

It is of singular interest that the concentration of lysozyme necessary to produce marked lethal and cytologic effects in the BCG strain of *M. tuberculosis* var. *bovis* is one hundred times as great as the concentration necessary to effect bacteriostasis.

SUMMARY

When young cells of the BCG strain of *M. tuberculosis* var. *bovis* were treated with 1,000 to 2,000 γ of lysozyme per ml. for forty-eight hours, the plate count of living organisms was reduced to approximately 1 per cent.

Concentrations of 2,000 γ of crystalline egg-white lysozyme per ml. were observed to exert marked cytologic effects on young cells of the BCG and Ravenel strains of *M. tuberculosis* var. *bovis* when allowed to act for periods of twenty-four to seventy-two hours. The characteristic cytologic changes are a lobulation and marked increase in the density of the cytoplasm to electrons and loss of the cell membranes. The cytoplasmic remains are insoluble and retain the property of acid-fastness.

Similar but less extensive cytologic changes resulted when living *M. tuberculosis avium* was subjected to the same treatment with lysozyme.

SUMARIO

Efectos Letales y Citológicos del Lisozima sobre los Bacilos Tuberculosos

Cuando se trató a células jóvenes de la cepa BCG del *M. tuberculosis* var. *bovis* con 1,000 a 2,000 γ de lisozima por ml. durante cuarenta y ocho horas, la numeración en placas de gérmenes vivos se redujo aproximadamente a 1 por ciento.

Observóse que las concentraciones de 2,000 γ de lisozima cristalino de clara de huevo ejercían decididos efectos citológicos sobre las células jóvenes de las cepas BCG y Ravenel del *M. tuberculosis* var. *bovis*, cuando se dejaban obrar por periodos de veinticuatro a setenta y dos horas. Las típicas alteraciones citológicas consisten en lobulación y mucho aumento del espesor del citoplasma a los electrones y pérdida de las membranas celulares. Los restos citoplásmicos son insolubles y retienen la propiedad acidorresistente.

Notáronse alteraciones citológicas semejantes, pero menos extensas, cuando se sometieron *M. tuberculosis avium* vivos al mismo tratamiento con lisozima.

RESUME

Effets de la lysozyme sur la létalité et la cytologie des bacilles tuberculeux

Il a été observé que, quand des jeunes cellules de la souche BCG de *M. tuberculosis* var. *bovis* sont traitées pendant quarante huit heures avec 1.000 à 2.000 γ de lysozyme par ml., le nombre des bacilles vivants est réduit d'environ 1%.

Des concentrations de 2.000 γ de lysozyme cristallisée blanc d'oeuf par ml. produisent des effets cytologiques marqués sur les cellules jeunes des souches BCG et Ravenel du *M. tuberculosis* var. *bovis*, quand elles sont soumises à leur action pendant vingt-quatre à soixante-douze heures. Les modifications cytologiques caractéristiques, visibles au microscope electronique, sont une lobulation et une augmentation marquée de la densité du cytoplasme électrons et la perte des membranes cellulaires. Les résidus cytoplasmiques sont insolubles et conservent la propriété d'acido-résistance.

Des changements cytologiques similaires mais moins extensifs se sont produits quand le *M. tuberculosis avium* vivant a été sormis à ce même traitement.

REFERENCES

(1) Myrvik, Q., and Weiser, R. S.: A tuberculostatic serum substance possessing lysozyme-like properties, Am. Rev. Tubere., 1951, *64*, 669.

(2) Corper, H. J.: Lysozyme and tuberculosis, Am. Rev. Tubere., 1932, *25*, 59.

(3) Wolff, L. K.: Untersuchungen über das lysozyme, Ztschr. f. Immunitatsforsch. u. exper. Therap., 1928, *54*, 188.

(4) BALDWIN, E. R.: Studies on tuberculous serums and the bacteriolysis of *Bacillus tuberculosis*, J. Med. Res., 1901, *12*, 215.

(5) KLING, C. A.: Untersuchungen uber die bakterientotenden eigenschaften der wissen blutkorperchen, Ztschr. f. Immunitatsforsch. u. exper. Therap., 1910, *7*, 1.

(6) KIRCHNER, O.: Besitzen tuberkulose- und nicht tuberkulosera ein bakterizides vermögen gegenüber dem tuberkelbazillus, Ztschr. f. Immunitatsforsch. u. exper. Therap., 1932, *74*, 55.

(7) HANKS, J. H., AND EVANS, B.: The action of serum, cells and blood on acid-fast bacteria *in vitro*, Am. Rev. Tubere., 1940, *41*, 605; 1940, *41*, 620; 1940, *41*, 637.

(8) HEDVALL, E.: Ein beitrag zur frage de mechanismus der immunität gegen tuberkulose, Svenska läk.-sällsk. förhandl., 1930, *56*, 1.

(9) MARTENSTEIN, H.: Wirkung von seren tuberkuloser auf tuberkelbazillen, Arch. Dermat. & Syph., 1926, *151*, 105.

(10) KALLOS, P., AND NATHAN, E.: Ueber die einwirkung von sera Hauttuberkuloser auf humane Tuberkulosebazillen in der Kirchnersechen Tiefenkultur, Arch. Dermat. & Syph., 1933, *167*, 343.

(11) GRIFFITH, A. S.: Further investigations on the strains of tubercle bacilli isolated from cases of lupus, J. Path. & Bact., 1914, *18*, 501.

(12) PAGEL, W.: The bactericidal power of the blood serum as a means of differentiating a certain type of pulmonary tuberculosis, Tubercle, 1935, *16*, 256.

(13) PAGEL, W.: The effect of blood serum on the growth of tubercle bacilli in the depth of liquid media, J. Path. & Bact., 1940, *50*, 111.

(14) COURMONT, P., AND GARDERE, H.: Pouvoir bactericide des liquides de pleuresies tuberculeuses sur le bacille de Koch, Bull. Acad. de méd., Paris, 1928, *99*, 711.

(15) COURMONT, P., AND GARDERE, H.: Variations du pouvoir bactericide sur le bacille de Koch du serum sanguin, Bull. Acad. de méd., Paris, 1929, *101*, 767.

(16) COURMONT, P., AND GARDERE, H.: Action bactericide du serums sanguin des tuberculeux sur le bacille de Koch, Compt. rend. Soc. de biol., 1929, *101*, 817.

(17) COURMONT, P., AND GARDERE, H.: Proprieties bactericides et agglutinantes, pour le bacille de Koch, du serum sanguin des animaux sains, Compt. rend. Soc. de biol., 1930, *105*, 8.

(18) RIST, E., AND IONESCU, V.: Nouvelles recheroches experimentales sur les proprieties inhibitrices de certaines pleuresies tuberculeuses au cours de pneumothorax artificiel, Ann. méd., 1929, *26*, 302.

(19) BANNERMAN, R.: A quantitative method for determining the fate of tubercle bacilli implanted in human plasma, Brit. J. Exper. Path., 1927, *8*, 209.

(20) MEISSNER, G.: Bakterizide und entwicklungshemmende Wirkung des Blute auf Tuberkelbazillen; eine neue methode zu ihrer quantitativen messung, Centralbl. f. Bakt. I., 1928, *106*, 210.

(21) SONAK, M.: Die beziehungen zwischen entwicklungshemmenden Stoffen für Tuberkelbazillen und der tuberkulin Allergie, Centralbl. f. Bakt. I., 1930, *115*, 173.

(22) WRIGHT, A. E.: New methods for the study of the pathology and treatment of tuberculous diseases, Lancet, 1924, *2*, 218.

(23) LURIE, M.: On the mechanism of immunity in tuberculosis, J. Exper. Med., 1936, *63*, 923.

(24) LURIE, M.: Studies on the mechanism of immunity in tuberculosis, J. Exper. Med., 1939, *69*, 555.

(25) MAYAMA, A.: Influence of blood of leprosy patients on growth of some bacteria: Comparative study with phagocytosis and agglutination, The Reports of the Research Institute for Tuberculosis and Leprosy, Tohoku University, 1951, *3*, 113.

(26) HALLAUER, C.: Ueber das lysozym, Zentralbl. f. Bakt., 1929, *114*, 549.

(27) MEYER, K.: Currents in Biochemical Research, Interscience Publishers, New York, 1946, chap. 18, p. 277.

(28) Webb, M.: The action of lysozyme on heat-killed gram positive microorganisms, J. Gen. Microbiol., 1948, *2*, 260.
(29) Fleming, A.: On a remarkable bacteriolytic element found in tissue and secretions, Proc. Roy. Soc., Lond., sB, 1922, *93*, 306.
(30) Kigasawa, T.: Lysozymwirkungen des Eiereiweisses, Ztschr. f. Immunitatsforsch. u. exper. Therap., 1927, *54*, 155.
(31) Boasson, E. H.: On the bacteriolysis by lysozyme, J. Immunol., 1938, *34*, 281.
(32) Georgi, C. E., Milfetzer, W., Burns, L., and Heotis, J.: On the existence of a cell granule in a thermophilic bacterium, Proc. Soc. Exper. Biol. & Med., 1951, *76*, 598.
(33) Kern, R. A., Kingkade, M. J., Kern, S. F., and Behrens, O. K.: Characterization of the action of lysozyme on *Staphylococcus aureus* and on *Micrococcus lysodeikticus*, J. Bact., 1951, *61*, 171.
(34) Alderton, G., and Fevold, H. L.: Direct crystallization of lysozyme from egg white and some crystalline salts of lysozyme, J. Biol. Chem., 1946, *164*, 1.
(35) Dubos, R. J., and Middlebrook, G.: Media for tubercle bacilli, Am. Rev. Tubere., 1947, *56*, 334.
(36) Fleming, A., and Allison, V. D.: Observations on a bacteriolytic substance (lysozyme) found in secretions and tissues, Brit. J. Exper. Path., 1922, *3*, 252.

COLLAPSE THERAPY FOR TUBERCULOUS PSYCHOTIC PATIENTS[1,2,3]

GEORGE N. J. SOMMER, JR., ABRAHAM M. BALTER, HAROLD S. HATCH, AND HAROLD J. MUENDEL

(Received for publication May 27, 1952)

INTRODUCTION

Although the prevalence of tuberculosis among psychotic patients has been shown to be high and there has been an increasing literature for some years regarding its detection and control, there have been few reports concerning the clinical evaluation of tuberculous psychotic patients and their treatment. At the Veterans Administration Hospital, Lyons, New Jersey, and at the New Jersey State Hospital at Trenton, active programs of treatment for tuberculosis have been combined with detection and isolation projects for the patients since 1946. In the present report, the methods and results of treatment will be discussed. Suffice it to say at this time that the detection and isolation programs have been actively pursued and will be discussed in another report. Collapse and, more recently, resectional therapy have been used as adjuncts to sanatorium care carried out similarly to that in institutions for tuberculosis of nonpsychotic patients. The details of sanatorium care will not be discussed other than to say that bed rest can be carried out quite satisfactorily with most psychotic patients. Antimicrobial therapy has been used according to the methods developed during the period of the work. A short discussion of the prevalence of tuberculosis in institutions for psychotic patients will be given to orient the readers in regard to the extent of the tuberculosis problem in these hospitals.

PREVALENCE OF TUBERCULOSIS AMONG PSYCHOTICS

There are a number of reports available which discuss the prevalence of tuberculosis in mental hospitals based upon roentgenographic surveys. In table 1, data on the prevalence of active and inactive tuberculosis based upon more extensive studies are given. In the California State mental hospitals, the classification was based upon standard roentgenographic studies; while, in the Michigan State Hospital for the Criminally Insane and in the two hospitals of the present study, clinical, roentgenographic, and bacteriologic methods of evaluation have been used. The table shows that the prevalence of tuberculosis in the hospitals varied from 5.5 to 9.6 per cent, while active tuberculosis prevalence varied from 3.1 to 5.7 per cent. All of these figures of prevalence may seem to

[1] From the Veterans Administration Hospital, Lyons, New Jersey; and the New Jersey State Hospital, Trenton, New Jersey.

[2] Presented before the Medical Session, as part of the *Medical Session on Tuberculosis*, at the 48th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, on May 27, 1952.

[3] Presented with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

TABLE 1

PREVALENCE OF TUBERCULOSIS IN MENTAL HOSPITALS

PLACE	YEAR	NUMBER OF PATIENTS	CLINICAL CLASSIFICATION	TUBERCULOUS PATIENTS	
				Number	Per Cent
California State Mental Hospitals (6)*	1946–1947	25,914	Probably active	1,037	4.0
			Questionably active	637	2.4
			Probably inactive	463	1.8
				2,139	8.2
Michigan State Hospital for Criminally Insane (4)†	1947	1,310	Active	41	3.1
			Inactive	31	2.4
				72	5.5
Veterans Administration Hospital, Lyons†	1950	2,254	Active	108	4.8
			Inactive	93	4.1
				201	8.9
	1951	1,986	Active	113	5.7
			Inactive	69	3.9
				182	9.6
New Jersey State Hospital, Trenton†	1951	3,788	Active	134	3.5
			Inactive	175	4.7
				309	8.2
	1952	3,821	Active	149	3.9
			Inactive	170	4.5
				319	8.4

* Based on roentgenographic examination.

† Based on roentgenographic, clinical, and bacteriologic examinations.

TABLE 2

HOSPITAL DEATHS DUE TO TUBERCULOSIS

PLACE	YEAR	AVERAGE NUMBER OF PATIENTS	NUMBER OF TUBERCULOSIS DEATHS	NUMBER PER 100,000 PER YEAR
Veterans Administration Hospital, Lyons	1950	2,254	8	360.0
	1951	1,986	7	350.0
New Jersey State Hospital, Trenton	1950 (fiscal year)	3,692	41	1,110.0
	1951 (fiscal year)	3,762	33	875.0
State of New Jersey	1949			27.2
	1950			21.2

be very high. Only by the recognition of this high tuberculosis rate in mental hospitals will the importance of the problem be appreciated. Furthermore, the tremendous death rate from tuberculosis in two hospitals is presented in table 2. While death rates calculated for relatively small groups, such as the patients in two hospitals, are not statistically significant, the figures do indicate a death rate far higher than that for the state of New Jersey in the same period. At the New Jersey State Hospital, the number of tuberculosis deaths is increased by the transfer of psychotic patients with tuberculosis (often seriously ill) from smaller institutions for mental diseases or tuberculosis.

THERAPY

At the two hospitals an effort has been made to provide the same therapeutic measures as those used for nonpsychotic tuberculosis patients. This ideal was established with the beginning of the programs and has been continued. Quite naturally, some deviation has been necessary because of lack of cooperation by patients. Lambiotte, Washington, and Boza'is (5) believe that extensive collapse measures should not be used on patients with hopeless psychiatric problems. It is not considered that such a view is proper since good therapeutic results in advanced tuberculosis will be rare without permanent collapse by thoracoplasty or probably pulmonary excision. As will be shown, good results have been attained by such methods without an excessive incidence of complications. The present writers believe that an active therapeutic program must be carried on as an essential adjunct to detection and isolation of tuberculous patients in mental hospitals. Without the therapeutic program, interest in the other aspects of tuberculosis control will lag. Furthermore, it will be difficult to interest the nursing and nonprofessional staff in the care of tuberculous patients who are not being actively treated.

Phrenic Nerve Paralysis

At the onset of the treatment program, it was natural to use the seemingly simpler collapse measure. Temporary phrenic nerve paralysis was used in 34 cases without any striking therapeutic results. In several it was employed when artificial pneumothorax was being abandoned and, in a few others, as an adjunct to pneumoperitoneum treatment. Except in the last group, phrenic nerve paralysis has been given up. Lambiotte, Washington, and Bozalis (5) had similar results. Isbister and associates (4) found phrenic nerve paralysis to be without value since their patients would not observe bed rest.

Artificial Pneumothorax

In discussion of artificial pneumothorax and thoracoplasty, a comparison will be made of the patients treated at the Veterans Administration and the New Jersey State hospitals with a group of patients from the Donnelly Memorial Hospital, a 125-bed municipal tuberculosis sanatorium. Thoracoscopy and thoracoplasty for these patients was carried out at the St. Francis Hospital. The two groups of patients were treated during the same period of time and from the

same therapeutic viewpoint. Such a comparison should be of value in evaluating the results of treatment of psychotic patients and also the problems of treatment.

Isbister and associates (4) do not believe that artificial pneumothorax is a measure suitable in their hands for psychotic patients and have abandoned the procedure. Close, West, and Glover (2) believe that pneumothorax can be carried out in psychotic patients without special difficulty. The most enthusiastic discussion of pneumothorax in psychotic patients is that of Lambiotte, Washington, and Bozalis (5), who did not find that the patients' psychoses presented a serious problem in pneumothorax management.

Pneumothorax was attempted in 74 patients, 5 of whom had bilateral pneumothorax. In table 3 are presented data regarding the age and sex of the Veterans Administration and New Jersey State hospitals' patients, with corresponding data from the Donnelly Memorial and St. Francis hospitals. The predominantly

TABLE 3

PNEUMOTHORAX: SEX AND AGE DATA

	VETERANS ADMINISTRATION HOSPITAL; NEW JERSEY STATE HOSPITAL	DONNELLY MEMORIAL HOSPITAL; ST. FRANCIS HOSPITAL
Total cases	74*	118†
Male	62	47
Female	12	71
Age in years		
High	71.0	64.0
Low	18.0	16.0
Average	42.5	29.6
More than 50	21.0	4.0

* 5 bilateral.
† 11 bilateral.

male distribution in the psychotic patients is enhanced by the absence of female patients at the Veterans Administration Hospital. It is further shown that the age distribution of the psychotic group is much higher than that of the control group. The average age of the psychotic group is 42.5 years compared with 29.6 in the control. Twenty-one psychotic patients of the 74 were more than fifty years of age, a rather large proportion compared with 4 of 118 in the control group. The average age of the pneumothorax-treated patients of Lambiotte, Washington, and Bozalis (5) is similarly high; 23 of their 33 patients were more than fifty years of age.

In table 4 are the data regarding thoracoscopy and pneumonolysis in the psychotic and control groups. It is evident that a much larger proportion of the nonpsychotic patients were suitable for thoracoscopy and pneumonolysis. In most of the patients of the Veterans Administration and New Jersey State hospitals, either no pneumothorax could be induced or the collapse was so limited as to contraindicate thoracoscopy. When the operation was carried out, the results of pneumonolysis were approximately the same in the two groups, with

43.8 per cent complete pneumonolysis in the psychotic patients and 51.3 per cent in the control group. The proportions of incomplete pneumonolyses were approximately the same, with a greater proportion of simple examination in the psychotic group. There were no complications in either group directly attributable to the operation. Lambiotte, Washington, and Bozalis (5) have had rather similar results with thoracoscopy. They advocate sodium pentothal anesthesia, in contrast with the local anesthesia used without incident in the present series. In their group, thoracoscopy and pneumonolysis were successfully carried out in eleven of thirty-three patients.

TABLE 4

PNEUMOTHORAX-THORACOSCOPY

	VETERANS ADMINISTRATION HOSPITAL; NEW JERSEY STATE HOSPITAL	DONNELLY MEMORIAL HOSPITAL; ST. FRANCIS HOSPITAL
Total cases	74	118
Patients with thoracoscopy*	19* (21.6%)	105† (89.0%)
Complete pneumonolysis	9 (43.8%)	39 (51.3%)
Partial pneumonolysis	8 (38.1%)	45 (39.1%)
Examination only	4 (18.1%)	11 (9.6%)

* 2 bilateral; 21 operations.
† 10 bilateral; 115 operations.

TABLE 5

PNEUMOTHORAX COMPLICATIONS

	VETERANS ADMINISTRATION HOSPITAL; NEW JERSEY STATE HOSPITAL	DONNELLY MEMORIAL HOSPITAL; ST. FRANCIS HOSPITAL
Total cases	74*	118†
Spontaneous pneumothorax	1 (decortication)	1 (death)
Empyema	2	2
Unexpandable lung	0	0

* 2 bilateral.
† 11 bilateral.

In table 5 are presented data regarding complications of pneumothorax. One spontaneous pneumothorax occurred in each group. The psychotic patient was successfully treated with decortication. In the nonpsychotic patient, a pneumothorax was attempted in an effort to control tuberculous disease in one lung as a preliminary to a thoracoplasty for very extensive contralateral tuberculosis. This "poor risk" patient died of spontaneous pneumothorax. Empyema occurred in 2 patients of each group. In 3 patients, empyema was diagnosed by culture of tubercle bacilli from clear pleural fluid, while in one psychotic patient the fluid was purulent in addition. No collapsed lungs have failed to re-expand. There have been no serious complications of pneumothorax therapy in the psychotic patients as a result of a policy of maintaining no pneumothoraces not completely anatomically successful or in the face of persistent pleural effusion.

The results of pneumothorax are presented in table 6. Only 14 of 71 patients (18.7 per cent) attained satisfactory collapse which was maintained for twelve months or more. In contrast, 71 (60.2 per cent) of the control group had successful pneumothorax for twelve months or more; complete follow-up data on this group are not available for further comparison. In one patient the successful collapse was bilateral. In 8 patients, inactive status with sputum and gastric contents negative for tubercle bacilli has been attained. One patient is dead of tuberculosis. Four living patients are excreting tubercle bacilli; 2 of these are included in the group with pneumothorax which is being continued in the hope of obtaining permission for contralateral therapy to control open lesions. One pneumothorax has been maintained with controlled tuberculous disease for more than twelve months. There are 2 other patients now receiving pneumothorax recently induced with satisfactory collapse. Thus, only 5 patients are now receiving pneumothorax therapy in the two hospitals.

TABLE 6

PNEUMOTHORAX RESULTS

	VETERANS ADMINISTRATION HOSPITAL; NEW JERSEY STATE HOSPITAL	DONNELLY MEMORIAL HOSPITAL; ST. FRANCIS HOSPITAL
Total cases	71	118
Satisfactory anatomical collapse; duration more than 12 months	14* (18.7%)	71† (60.2%)
Inactive (lung re-expanded)	8	
Sputum positive for tubercle bacilli	4	
Dead	1	
Pneumothorax continued	3‡	

* 1 bilateral.

† 5 bilateral.

‡ 2 also listed as sputum positive for tubercle bacilli.

In review, the results attained by therapeutic pneumothorax have not been strikingly satisfactory. Sufficient success has been obtained, however, to warrant its continued use in more carefully selected patients. The numerous instances in which collapse was not successful reflect the rather advanced average age of the patients and the incidence of chronic tuberculous disease. A far greater proportion of successful collapse was attained in the younger "control" group. To some extent the high proportion of unsuccessful pneumothorax was due to the effort, early in the work, to use a seemingly simple measure and, in part, to lack of patient cooperation.

Pneumoperitoneum

Pneumoperitoneum has been instituted thirty-five times and is now being maintained in 11 patients. One patient has been discharged from the hospital and has remained well. In 2 cases at the Veterans Administration Hospital the pneumoperitoneum is being maintained in an effort to control contralateral tuberculous disease following thoracoplasty, one of which was performed elsewhere. The

remaining 9 pneumoperitoneums are being maintained at the New Jersey State Hospital for rather severe bilateral tuberculosis. The favorable results with pneumoperitoneum have been, with the exception noted, of a palliative nature.

Thoracoplasty

It was with some misgivings that the first extrapleural thoracoplasty was planned in July, 1946. This patient (Case 1) had an eight-rib, three-stage thoracoplasty without special incident. Since then 50 additional patients have been operated upon at the two hospitals. The group will be compared with a group of 62 patients from the Donnelly Memorial and St. Francis hospitals.

In table 7 are presented sex and age data from the psychotic and nonpsychotic groups. In the former, the very low incidence of operations on women is due to the entirely male population in the Veterans Administration Hospital. The

TABLE 7

THORACOPLASTY: SEX AND AGE DATA

	VETERANS ADMINISTRATION HOSPITAL; NEW JERSEY STATE HOSPITAL	DONNELLY MEMORIAL HOSPITAL; ST. FRANCIS HOSPITAL
Total cases	51	62
Sex		
Male	48	25
Female	3	37
Age in years		
High	71.0	57.0
Low	25.0	19.0
Average	45.4	32.7
More than 50	25.0	6.0

group from Donnelly Memorial and St. Francis hospitals is predominantly female. There seem to be marked differences in the sex composition of thoracoplasty series reported in the literature since in that of Rubin and Klopstock (7) males predominate, while in that of Gutheil and associates (3) the two sexes were almost equal in number. There is a striking difference in age between the psychotic and nonpsychotic groups as seen in table 7. The average age of the psychotic patients treated by thoracoplasty is 45.4 years in contrast to 32.7 years in the nonpsychotic patient. Twenty-five, almost 50 per cent, of the psychotic patients were more than fifty years of age in contrast to approximately 10 per cent in the other group. Lambiotte, Washington, and Bozalis (5) found a similar age distribution in their eleven psychotic patients treated by thoracoplasty; their patients ranged in age from 25 to 57 years, with an average age of 47 years. In further contrast to the large percentage of patients more than 50 years of age in the psychotic group, only 13 of 168 patients of Rubin and Klopstock (7) and 8 of 254 patients of Gutheil and associates (3) were more than 50 years of age.

Rubin and Klopstock (7) have pointed out that the results attained by thoracoplasty have a relationship to the type of tuberculous disease present. Using

their classification, a comparison (table 8) has been made of the types of disease in the psychotic patients with those from the Donnelly Memorial and St. Francis hospitals and with two other thoracoplasty groups. The patients of the Veterans Administration and New Jersey State hospitals had more predominantly fibrocaseous tuberculosis than did the patients of the other three groups. More than 84 per cent of the psychotic patients had the presumably favorable fibrocaseous

TABLE 8

THORACOPLASTY: TYPE OF DISEASE

	VETERANS ADMINISTRATION HOSPITAL; NEW JERSEY STATE HOSPITAL	DONNELLY MEMORIAL HOSPITAL; ST. FRANCIS HOSPITAL	RUBIN AND KLOPSTOCK (7)	GUTHEIL *et al.* (3)
Total cases	51	62	168	254
Fibrocaseous	43 (84.3%)	46 (74.2%)	117 (69.7%)	137 (53.9%)
Fibroid	7 (13.7%)	10 (16.1%)	13 (7.7%)	27 (10.6%)
Caseocavernous	1	5	5	15
Giant cavity		1	23	45
Other			10	30

TABLE 9

THORACOPLASTY: EXTENT OF DISEASE

	VETERANS ADMINISTRATION HOSPITAL; NEW JERSEY STATE HOSPITAL	DONNELLY MEMORIAL HOSPITAL; ST. FRANCIS HOSPITAL	GUTHEIL *et al.* (3)
Total cases	51	62	254
Ipsilateral			
Moderately advanced	39	23	
Far advanced	12	39	
Contralateral			
Total significant	28 (54.9%)	37 (59.7%)	194 (76.4%)
Minimal	19	15	
Moderately advanced	9	22	
Concurrent pneumothorax	1 (1.9%)	16 (25.9%)	38 (14.9%)
Post-thoracoplasty pneumothorax		2	14*

* Extrapleural pneumonolysis and paraffin filling in 11 additional cases.

tuberculosis. The percentage of fibroid tuberculosis was relatively similar in the four series. Fibrocaseous and fibroid tuberculosis affected practically the entire group in the Veterans Administration and New Jersey State hospitals.

In table 9 data are presented in regard to the extent of tuberculous disease in the lung to be collapsed and in the contralateral lung. Moderately advanced tuberculosis predominated in the lung to be collapsed by thoracoplasty in the psychotic patients in contrast to the high incidence of far advanced disease in the nonpsychotic group from the Donnelly Memorial and St. Francis hospitals. In considering the contralateral lung, the two groups had similar percentages of

significant tuberculous disease, with figures of 54.9 and 59.7 per cent in the psychotic and nonpsychotic groups, respectively. On the other hand, the patients in the Donnelly Memorial and St. Francis hospitals had more extensive contralateral disease as is seen in the greater relative number of moderately advanced cases. Furthermore, concurrent pneumothorax was carried out in only one patient in the Veterans Administration Hospital in contrast to the 25.9 per cent incidence in the group in the Donnelly Memorial and St. Francis hospitals. Gutheil and associates (3) report an incidence of significant contralateral disease of 76.4 per cent. While the incidence of concurrent pneumothorax is considerably lower than in the group in the Donnelly Memorial and St. Francis hospitals. Gutheil and associates (3) carried out post-thoracoplasty contralateral collapse in a good percentage of their cases.

TABLE 10

THORACOPLASTY: EXTENT

RIBS REMOVED	VETERANS ADMINISTRATION HOSPITAL; NEW JERSEY STATE HOSPITAL	DONNELLY MEMORIAL HOSPITAL; ST. FRANCIS HOSPITAL
Total cases	51	62*
Three	1	
Four		1
Five	7	2
Six	1	
Seven	35	50
Eight	7	6
Nine		3

* Extrafascial apicolysis in 2.

In spite of the effort made through the tables to present a concise comparison of a group of nonpsychotic patients subjected to collapse therapy from standpoints of age and extent of disease, a further general statement is necessary. It may be stated that the psychotic tuberculous patients, as a whole, represent an older group with more chronic tuberculosis than the nonpsychotic. That severe fatal tuberculosis, both acute and chronic, is only too common among the psychotic patients has already been shown. The treated patients in general have had less acute and extensive disease than the nonpsychotic group. On the other hand, however, their general physical condition and nutrition were not nearly as good as in the nonpsychotic patients.

Data on the extent of thoracoplasty are presented in table 10. The majority of operations, all of which were carried out as described by Alexander (1), were of seven ribs in both groups. Experience has shown the value of small, that is, two- and one-half-rib stages in the psychotic patients. From the experience in patients treated, the removal of more ribs at one stage in psychotic patients is not recommended. Close, West, and Glover (2) have pursued a similar course of small stages in their eight cases, while Lambiotte, Washington, and Bozalis (5) have used two-stage thoracoplasty but with two deaths in eleven patients.

Data on the complications of thoracoplasty are presented in table 11. Severe wound infection occurred considerably more frequently in the psychotic group than in the nonpsychotic group. It is interesting to note that in the nonpsychotic patients only one mild infection occurred in 42 patients whose wounds were closed with fine cotton sutures. A similar success was not achieved in the psychotic patients when cotton rather than catgut sutures were used. The incidence of atelectasis without spread of tuberculous disease and the incidence of postoperative spread of tuberculous disease were approximately double in the psychotic group compared with the control group. The atelectasis and spread of disease in the groups in the Veterans Administration and New Jersey State hospitals are certainly greater than those reported generally in thoracoplasty patients. Only one death occurred postoperatively in each group. The psychotic patient died of atelectasis and bilateral spread of tuberculous disease, while the

TABLE 11

THORACOPLASTY: OPERATIVE COMPLICATIONS

	VETERANS ADMINISTRATION HOSPITAL; NEW JERSEY STATE HOSPITAL	DONNELLY MEMORIAL HOSPITAL; ST. FRANCIS HOSPITAL	RUBIN AND KLOPSTOCK (7)
Total cases	51	62	168
Wound infection			
Severe	6 (11.8%)*	2 (3.2%)	25 (14.9%)
Mild		2†	(severity not stated)
Atelectasis (no spread)	5 (9.8%)	3 (4.6%)	
Spread of disease	6 (11.8%)	4 (6.6%)	19 (11.3%)
Death	1 (1.9%)	1 (1.6%)	9 (5.3%)

* 2 severe infections in 8 cases with catgut sutures.

† 1 mild infection only in 42 cases with cotton sutures.

control patient died of dyspnea following a secondary thoracoplasty with contralateral pneumothorax. The incidence of all forms of complications following operation in the psychotic patients compares very favorably with the incidence in the report of Rubin and Klopstock (7).[4]

The following case reports are illustrative of the type of case treated.

Case Reports

Case 1. E. W., a 30-year-old white woman, had been a patient in the New Jersey State Hospital since 1933. She was known to have tuberculosis for some years with tubercle bacilli consistently demonstrated in the sputum. Roentgenograms showed cavernous, far advanced right pulmonary tuberculosis. An eight-rib, three-stage thoracoplasty was carried out, beginning July 24, 1946, and was completed on August 28. The patient was very cooperative throughout. Fluid had to be aspirated from the wound several times following

[4] The fifty-second psychotic thoracoplasty patient died of paradoxical movement eleven days following the first-stage operation; the operation was performed following the preparation of this paper.

the first-stage operation. The patient has remained well since operation. Cultures of gastric contents have failed to disclose tubercle bacilli on many occasions, including January and February, 1952. Roentgenograms taken in 1952 show an excellent eight-rib collapse.

The outcome in this case illustrates how simple and successful may be the course of staged thoracoplasty in a psychotic patient.

Case 2. L. M., a 42-year-old white man, was admitted to the Veterans Administration Hospital on June 29, 1947. He was known to have had pulmonary tuberculosis since 1938. Roentgenographic studies demonstrated bilateral pulmonary tuberculosis; tubercle bacilli were persistently found in his sputum. After improvement in his right-sided lesions, a left thoracoplasty was advised. First-stage thoracoplasty was performed with resection of two and one-half ribs and the second and third transverse processes on November 2, 1949. Marked paradoxical movement was present postoperatively. His temperature rose to 104°F. on November 4. The patient was uncooperative; a wet, unproductive cough was present. Endotracheal catheter suction was carried out successfully on November 4, but the patient refused to cooperate for further aspiration. Bronchoscopic aspiration was performed on November 8 with some difficulty. The atelectasis progressed to extensive ipsilateral spread of tuberculous disease. Streptomycin therapy was commenced and continued, 1 gm. daily for 87 days. Under antimicrobial therapy and further supportive treatment, the new disease progressively cleared. The second- and third-stage operations were carried out and completed with removal of eight ribs in all on December 21, 1949. The patient has done well since operation. Cultures of gastric contents have been negative for tubercle bacilli since the early part of 1951 and have remained so during 1952. A recent roentgenogram showed a satisfactory collapse of the left lung by thoracoplasty and apparently controlled lesions in the right lung.

This case represents the extreme difficulty which may be met in the postoperative care of a psychotic patient. This man was powerful and uncooperative. Each measure to remove his sputum could be carried out only one time. Without streptomycin therapy it is doubtful that his extensive new lesions could have been controlled.

In these patients streptomycin has been used preoperatively only in the presence of what has been regarded as acute tuberculous disease. It has been used during thoracoplasty and later, when indicated because of spread of disease. In all likelihood, the policy of Isbister and associates (4), who gave streptomycin to their eight thoracoplasty patients for sixty days during the course of operations, would have been worth while. Streptomycin was used only twice in preparing patients for thoracoplasty and eleven times during and after operation because of atelectasis or spread, real or suspected. With the use of combined intermittent therapy of the present day, it is likely that chemotherapeutic preparation for thoracoplasty should be more freely employed.

Late results of thoracoplasty: In table 12 are assembled the data concerning the late results of thoracoplasty for pulmonary tuberculosis. Follow-up studies are given concerning only 35 patients operated upon prior to January, 1951. The follow-up period is calculated in months up to January 1, 1952, even though the last cultural studies of sputum and gastric contents of these patients were made during 1952. The period of follow-up for 31 living patients varies from 12 to 64 months, with an average of 26.4 months. Sixteen living patients have been followed for less than 12 months up to January 1, 1952.

One postoperative death has already been described. One patient died six months after an apparently satisfactory thoracoplasty of a fulminating exacerbation of tuberculosis. There have been 2 deaths of nontuberculous causes in patients who were apparently doing well following thoracoplasty. One patient died of myocardial infarction eight months after operation; and another, of perforation of a duodenal ulcer seven months following operation. Post-mortem examination of this patient showed an adequate collapse of the lung by the thoracoplasty. Three patients are recorded as having demonstrable tubercle bacilli in their discharges. One has a contralateral, small tension cavity uncontrolled by pneumoperitoneum and antimicrobial therapy; the patient is unsuitable for a contralateral operation. A second patient was found to have tubercle bacilli by culture of sputum two years following thoracoplasty. The third patient had an upper lobe lobectomy for a persistent cavity in June, 1951. While this patient is doing well, because of the short follow-up after lobectomy he is listed

TABLE 12

THORACOPLASTY RESULTS

	VETERANS ADMINISTRATION HOSPITAL; NEW JERSEY STATE HOSPITAL	DONNELLY MEMORIAL HOSPITAL; ST. FRANCIS HOSPITAL
Total cases	51	62
Operative death	1	1
Late tuberculosis deaths	1	5
Late nontuberculosis deaths	2	2
Post-thoracoplasty resections	1*	4
Positive for tubercle bacilli	3	
No bacteriologic check-up	1	
Negative for tubercle bacilli	27 (77.1%)	
Operation less than 12 months ago	16	

* Also listed as positive for tubercle bacilli.

among the "sputum-positive" cases and recorded twice in table 12. In one patient, bacteriologic studies have been impossible since operation because of complete lack of cooperation. It has not been thought justifiable to bronchoscope this patient with sodium pentothal anesthesia to obtain a sputum specimen.

Thirty-five patients were operated upon prior to January, 1951. Twenty-seven (77.1 per cent) have secretions negative for tubercle bacilli, examined by repeated culture of sputum and fasting gastric contents. Of 31 living patients, the percentage of "negative" cases is 87.1 per cent. Rubin and Klopstock (7) had favorable results in 76.8 per cent of their patients. Gutheil and associates (3) found secretions negative for tubercle bacilli in 76 per cent after thoracoplasty, with an additional 4 per cent inactive after pulmonary resection. The follow-up period in these two reports is, of course, longer than in the present one. Unfortunately follow-up data are not complete on the patients in Donnelly Memorial and St. Francis hospitals. There were in this last group, however, more late deaths due to tuberculosis and more post-thoracoplasty resections. The differ-

ence is explained by the fact that more severely ill patients were operated upon in the group in these two hospitals. It is believed that the results attained with thoracoplasty in the psychotic patients compare quite satisfactorily with the results in two recent articles from the literature.

Successful thoracoplasty cannot be considered a form of treatment for psychoses. Three patients with secretions negative for tubercle bacilli, however, have been adjudged to have recovered sufficiently from their psychoses to warrant discharge on trial.

Pulmonary Resection

Since June, 1951, 6 patients have been treated for pulmonary tuberculosis by pulmonary resection. The first lobectomy was for a thoracoplasty failure with a persistent cavity. In the second case, local resection of two caseous foci with persistent "positive" sputum was carried out. Two successful upper lobe lobectomies, one combined with middle lobe lobectomy, were carried out for lesions thought possibly due to bronchial cancer but shown pathologically to be due to active tuberculosis. Most recently, a segmental upper lobe lobectomy and another local resection have been performed. The early results of these operations have been good. During 1948 a right pneumonectomy was done for extensive parenchymal tuberculosis with active tuberculous bronchitis; this patient died postoperatively due to tracheal damage with an unsatisfactory repair.

The satisfactory mortality rate and early results of pulmonary resection in the small group described indicate that this method of treatment is feasible for psychotic patients. Stringer (8) has had similar good results and finds, as do the present writers, that pulmonary resection is being used to a greater extent in his work with psychotic than with nonpsychotic patients. It does seem likely that resection will complement thoracoplasty to a great extent with these patients if it does not replace it. Certainly, pulmonary resection should be given a thorough trial. In the most recently performed thoracoplasty, pulmonary atelectasis occurred following the first-stage operation; after the second stage, atelectasis and spread of disease took place. This patient would not cough at all after operation although he was pleasant and otherwise cooperative. It may have been that a pulmonary resection would have obviated the spread of disease in this patient.

It is interesting to note that the average age of the 6 patients treated with lobectomy was 46.3 years. Three were more than 50 years of age, the oldest being 62 years of age.

SUMMARY

A study has been made of psychotic patients treated for pulmonary tuberculosis. Treatment can be successfully carried out and is a necessary part of tuberculosis control and isolation programs in hospitals for the mentally ill in which high prevalence and death rates due to tuberculosis are the rule. The well-established principles of sanatorium care and bed rest are applicable to psychotic patients. Phrenic nerve paralysis has had little beneficial effect in the psychotic

patients treated. Artificial pneumothorax can be carried out with patient cooperation. As many of these patients are in the older age groups, pneumothorax has a limited, though definite, field of application. Pneumoperitoneum is of value combined with antimicrobial therapy of extensive tuberculous disease. The best results have been attained with extrapleural thoracoplasty. These results compare favorably with results reported in the literature in modern series of cases. Thoracoplasty has been carried out in 51 patients, with a case mortality rate of 1.9 per cent but a higher morbidity rate than in a comparable group of nonpsychotic cases. The early results of a small group of patients treated by pulmonary resection are encouraging. It is likely that pulmonary resection will take its place with thoracoplasty as a suitable method of treatment in tuberculosis in psychotic patients and may largely replace it.

SUMARIO

La Colapsoterapia en los Psicóticos Tuberculosos

Este estudio versa sobre psicóticos tratados por tuberculosis pulmonar. El tratamiento puede llevarse a cabo con éxito y constituye parte necesaria de la lucha antituberculosa y los planes de aislamiento en los hospitales para los enfermos mentales, en quienes son altas, por regla general, la incidencia y la mortalidad tuberculosas. Los principios bien establecidos de la asistencia sanatorial y del reposo en cama tienen igualmente aplicación a los psicóticos. La parálisis del frénico ha mostrado muy poco efecto en los psicóticos tratados con ella. El neumotórax terapéutico puede ejecutarse si el enfermo coopera; como muchos de esos pacientes corresponden a las edades más avanzadas, el neumotórax tiene una esfera de aplicación limitada, pero bien definida. El neumoperitoneo es de valor, combinado con la antibioticoterapia de la afección tuberculosa. Los mejores resultados fueron obtenidos con la toracoplastia extrapleural, comparándose con los descritos en series recientes de casos en la literatura. La toracoplastia fué llevada a cabo en 51 enfermos, con una mortalidad de 1.9 por ciento, pero con una morbidad mayor que un un grupo comparable de casos no psicóticos. Los resultados tempranos en un grupito de enfermos tratados con la resección pulmonar son buenos. Parece probable que la resección pulmonar tomará su puesto con la toracoplastia como método adecuado de tratamiento de la tuberculosis en los psicóticos y quizás suplante en gran parte a la última.

RESUME

Collapsothérapie pour tuberculose chez les malades mentaux

Des malades atteints de maladies mentales et traités pour tuberculose pulmonaire ont été l'objet d'une étude. Le traitement peut être pratiqué avec succès et il représente une partie nécessaire de la lutte antituberculeuse et des programmes d'isolement dans les hôpitaux réservés aux malades mentaux, et dans lesquels des taux élevés de fréquence et de mortalité sont la règle. Les principes bien établis de la cure sanatoriale et de repos au lit s'appliquent aux malades mentaux. Chez ces malades, la paralysie du nerf phrénique n'a guère donné de résultats. Le pneumothorax artificiel peut être instauré avec la coopération du malade; comme un grand nombre de ces malades appartient aux groupes d'âge plus avancé, le pneumothorax a un champ d'application limité, mais net.

Le pneumopéritoine se montre utile lorsqu'il est associé à la thérapie antibiotique de l'affection tuberculeuse extensive. Les meilleurs résultats ont été obtenus avec la thoracoplastie extra-pleurale. Ces résultats peuvent se comparer favorablement avec ceux rapportés dans la littérature pour les séries de cas étudiées à présent. La thoracoplastie a été effectuée chez 51 malades avec un taux de mortalité de 1.9 pour cent, mais avec un taux

de morbidité plus élevé que dans un groupe comparable de malades non affectés de psychose. Les résultats immédiats d'un petit groupe de malades traités par résection sont bons. Il est probable que la résection pulmonaire prendra rang avec la thoracoplastie comme une méthode appropriée au traitement de la tuberculose des malades mentaux et susceptible de la remplacer dans une large mesure.

REFERENCES

(1) Alexander, J.: The Collapse Therapy of Pulmonary Tuberculosis, Charles C Thomas, Springfield, Illinois, 1937.

(2) Close, H. P., West, B. M., and Glover, R. P.: Unpublished data, 1950.

(3) Gutheil, D., Steele, J. D., Cadden, A. V., and Sakaguchi, S.: The late results of thoracoplasty according to type of pulmonary tuberculosis, Am. Rev. Tuberc., 1950, *62*, 645.

(4) Isbister, J. L., Robertson, P. C., Stanley, A. L., and Stringer, C. J.: A tuberculosis control program in a mental institution, J. Michigan M. Soc., 1951, *50*, 1251.

(5) Lambiotte, L. O., Washington, E. L., and Bozalis, G. S.: Management of tuberculosis in psychotic patients, Am. Rev. Tuberc., 1949, *59*, 289.

(6) Oechsli, W. R.: Tuberculosis and control program of nine California mental institutions, Pub. Health Rep., 1949, *64*, 4.

(7) Rubin, M., and Klopstock, R.: Influence of type of disease on the results of thoracoplasty in pulmonary tuberculosis, Am. Rev. Tuberc., 1949, *60*, 273.

(8) Stringer, C. J.: Personal communication, March 24, 1952.

Case Reports

HEPATIC TUBERCULOSIS IN A PATIENT WITH SICKLE-CELL ANEMIA WHO DIED OF FATAL POST-TRANSFUSION HEPATITIS[1,2]

EDWARD R. CHRISTIAN

(Received for publication August 8, 1952)

INTRODUCTION

With the advent of widespread application of needle biopsy of the liver, frequent reports of tuberculosis involving that organ have been appearing in the literature (1–5). Such reports lead to the belief that hepatic tuberculosis, of common occurrence in persons dying from pulmonary tuberculosis, also occurs more frequently than is supposed in persons with obscure, if demonstrable, pulmonary disease. In the past fourteen months the present writer has detected 4 cases of hepatic tuberculosis by means of needle biopsy. In 3 of the cases the existence of pulmonary disease had not been ascertained and liver biopsy was resorted to in an effort to establish definitive diagnoses. The fourth patient was undergoing treatment for pulmonary tuberculosis and oral histoplasmosis, but had neither clinical nor laboratory evidence of liver involvement. Needle biopsy of the liver, done in search for disseminated histoplasmosis, revealed a tuberculoma.

The purpose of the present paper is to report the case of one patient who had tuberculosis of the liver in addition to sickle-cell anemia and whose death was believed to have resulted from post-transfusion hepatitis which precipitated a terminal sickle-cell crisis. Histologic changes caused by the three disease processes were followed by means of serial biopsies of the liver. Such observations in sickle-cell anemia and tuberculous hepatitis have been few.

CASE REPORT

Z. F. (25954), a 32-year-old Negro male, was admitted to the Medical Service of the Veterans Administration Hospital, New Orleans, Louisiana, on August 10, 1951. He stated that he had been in excellent health until one month prior to admission, when he first noticed the onset of a severe cough which produced copious sputum streaked with blood. Although he had no chest pain, he complained of soreness in the epigastrium and right upper abdominal quadrant; coughing caused pain in those areas. He had daily fever, and on four occasions had experienced shaking chills. Drenching night sweats occurred frequently. Anorexia was pronounced, and the patient had lost 27 pounds in weight. Other complaints included malaise and marked weakness.

The patient's past history revealed that he had had frequent attacks of arthritis during his childhood. In 1942, while with the Armed Forces, he had been hospitalized for five months because of arthritis which involved his lower extremities. Later, while in the South Pacific, he had been hospitalized again because of arthritis accompanied by jaundice.

[1] From the Medical Service and Research Laboratory, Veterans Administration Hospital, New Orleans, Louisiana; and the Department of Medicine, The Tulane University of Louisiana, School of Medicine, New Orleans, Louisiana.

[2] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Family history was not contributory. The patient denied contacts with persons known to have tuberculosis.

Physical examination: Physical examination revealed an obviously ill man who was 63 inches in height and weighed 108 pounds. His oral temperature was 102°F.; blood pressure, 100 systolic and 70 diastolic in mm. of mercury; pulse rate, 110 per minute. He coughed frequently and expectorated large quantities of gray sputum; however, he did not appear to be in great distress. There was slight scleral icterus. Numerous coarse rales were audible in the upper portions of both lungs. The liver edge extended three inches below the right costal margin; the organ was smooth, more firm than usual, and somewhat tender to palpation. The spleen was not palpable, and there was no ascites. Small, discrete lymph nodes were felt in the epitrochlear, axillary, inguinal, and supraclavicular areas. A tracheal tug was present.

Laboratory studies: The leukocyte count was 12,450 per cu. mm., with a normal differential. Erythrocyte count was 2.91 millions per cu. mm.; hemoglobin, 10 gm. per 100 ml. The erythrocyte sedimentation rate was 23 mm. per hour. Urine was acid in reaction and had a specific gravity of 1.008; it was free from sugar but contained a trace of albumin. Microscopically, a few hyaline and granular casts and occasional pus cells were seen in each high-power field. Blood urea nitrogen was 8.9 mg. per 100 ml.; fasting blood glucose, 96 mg. per 100 ml.; serum chloride, 94 mEq. per liter; plasma HCO_3 content, 17 mEq. per liter. Tests of liver function were as follows: bromsulfalein retention, 14.4 per cent at 45 minutes; cephalin flocculation, 4 plus; total serum bilirubin, 2.56 mg. per 100 ml.; one minute bilirubin, 1.19 mg. per 100 ml.; thymol turbidity, 5.7 units; lipid turbidity, 600 mg. per 100 ml.; gamma globulin, 23 $ZnSO_4$ units; alkaline phosphatase, 4.8 units; prothrombin time, 17.6 seconds; total serum protein, 7.9 gm. per 100 ml.; albumin, 4.3 gm. per 100 ml.; globulin, 3.6 gm. per 100 ml.; urine urobilinogen (2 to 4 p.m.), 3.8 Ehrlich units.

The following studies were negative: examination of the urine for bile; blood smears for malarial organisms; serologic test for syphilis; examinations of feces for ova, cysts, and parasites; blood cultures; agglutination tests for typhoid, typhus, and brucellosis. Smears and cultures of sputum were positive for *Streptococci*, *Staphylococcus aureus*, and *Bacillus pyocyaneus*, but were negative for fungi and acid-fast bacilli. A roentgenogram of the chest revealed infiltrative lesions in both subapical regions and a mass in the right superior mediastinum. Abdominal roentgenograms were negative for evidence of calcification within the liver, spleen, and adrenal glands. The first-strength tuberculin skin test was positive, 1 plus. The electrocardiogram was normal.

Course in hospital: Figures 1 and 2 graphically correlate symptoms and signs with pertinent laboratory data. The patient had a spiking temperature curve after admission, the peaks ranging between 101° and 105°F. and falling to subnormal levels after the administration of acetylsalicylic acid. He continued to cough at frequent intervals and expectorated large quantities of sputum. Surprisingly, he never appeared as ill as his clinical record indicated. Suspected diagnoses included miliary tuberculosis, sarcoidosis, sickle-cell anemia, lymphoma, and post-necrotic cirrhosis; the mediastinal mass, because of the tracheal tug and transmitted pulsations noted at fluoroscopy, was also considered to be questionably aneurysmal in origin. In the absence of a definitive diagnosis, penicillin was administered empirically without effect. During the first week of hospitalization the patient received two 500 cc. transfusions of whole blood without adverse reaction. Efforts to arrive at a diagnosis included an unsuccessful attempt at biopsy of a supraclavicular lymph node.

A few days after admission to the hospital, examination of the peripheral blood showed 100 per cent sickling within four hours, and bone marrow studies likewise showed findings consistent with sickle-cell anemia.

By the end of the first week it was the consensus that miliary tuberculosis, though not proved, was the most likely diagnosis. Consequently, the patient was started on treatment with streptomycin, 2 gm. daily, and sodium para-aminosalicylate (PAS), 12 gm. daily. After one week of such treatment, the patient was subjected to needle biopsy of

the liver. Microscopic sections showed a caseous granuloma with a Langhans' plant cell (figure 3); the lesion was compatible histologically with tuberculosis. Some of the sinusoids were moderately distended with erythrocytes, many of which were sickled (figure 4). A few Kupffer cells were packed with phagocytized erythrocytes (figure 5). Special staining technique revealed no increase in hemosiderin.

The therapeutic effects of streptomycin and PAS were prompt and striking. After one week the patient stopped having night sweats; weakness subsided within two weeks, and malaise within three weeks. His cough became less severe and the quantity of sputum expectorated daily decreased from a maximum of 450 cc. to an average of 60 cc. Fever subsided by lysis and the patient's temperature was normal by the fourth week of treatment. His appetite improved, and a slight gain in weight was noted. A new sense of well-being made restriction of his physical activity difficult. During that period results of laboratory studies, in general, also reflected the favorable response to treatment. However, there was persistence of increased urine urobilinogen, slightly increased bilirubinemia, leukocytosis, anemia, and reticulocytosis. During the next several weeks serial roentgenograms of the chest demonstrated progressive reduction in the size of the mediastinal mass and disappearance of the subapical infiltrative lesions. Small nodules of calcific density appeared in both lungs. Although they resembled healed miliary tubercles, consideration was given to the possibility of their representing healed small infarcts which had resulted from sickle cell disease (6).

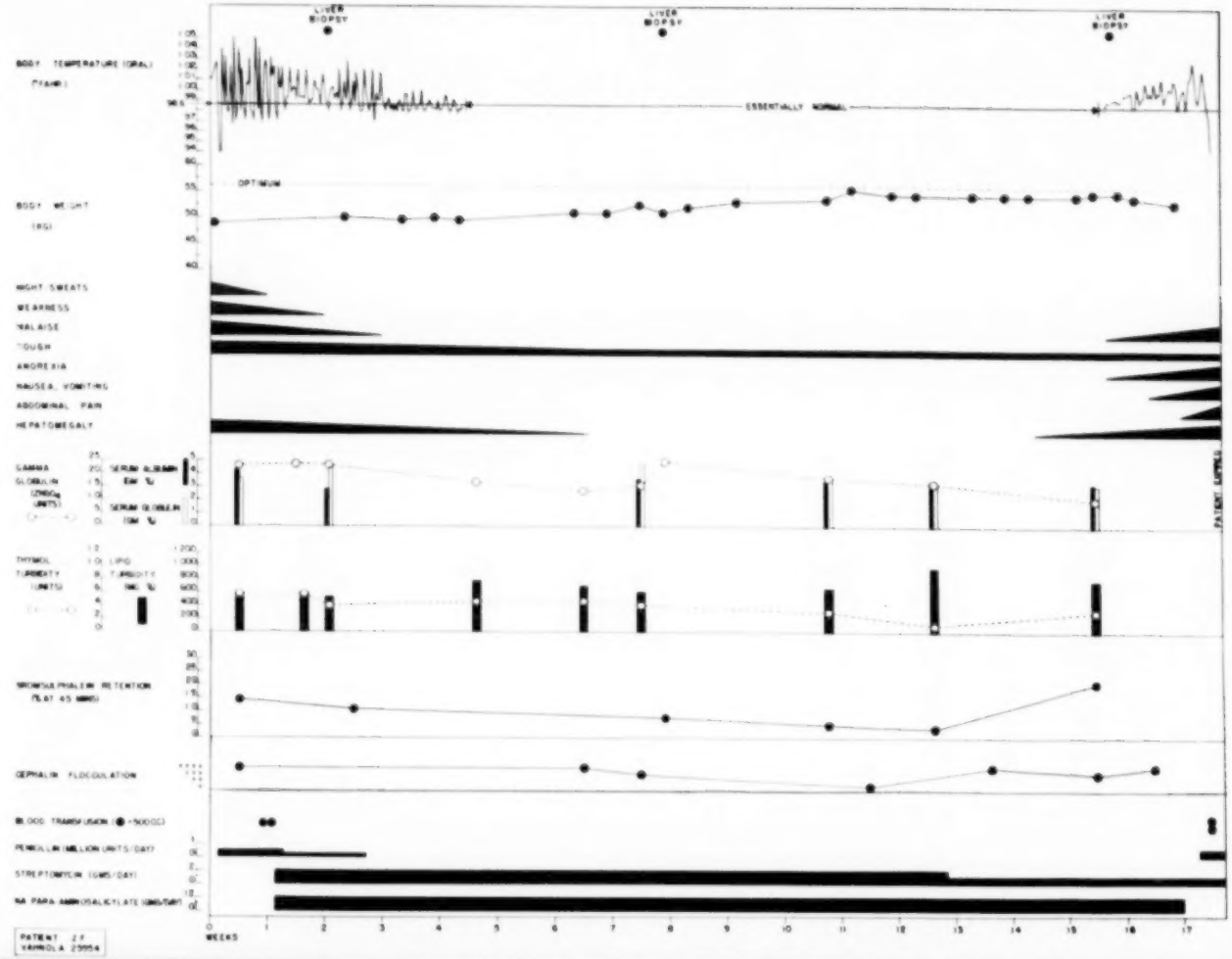
During the seventh week of treatment, needle biopsy of the liver was repeated. Microscopic sections showed small, nonspecific granulomas (figure 6) and evidence of sickle-cell disease previously described in the initial biopsy specimen (figures 4 and 5). At the time of the second biopsy, quantitative urobilinogen studies were accomplished for the first time during the patient's illness. The amount of fecal urobilinogen, 273 mg. in twenty-four hours, was at the upper limit of normal and was not conclusive evidence for or against a hemolytic process indicated by other laboratory findings, i.e., anemia, increased bilirubinemia, and reticulocytosis. The amount of urine urobilinogen was 243 mg. in twenty-four hours. A similar marked increase has been observed in one other patient who had tuberculous hepatitis and equivocal evidence of hemolysis (5). As the patient's condition continued to improve during the next few weeks, quantitative determinations of fecal and urine urobilinogen were repeated. Both decreased, but the amount of urine urobilinogen never became normal.

Early in the fourth month of treatment and at a time when the patient was feeling as well as usual, it was found that his liver was enlarging insidiously and that a progressive increase in serum bilirubin had begun. Those alarming signs occurred 103 days after a blood transfusion had been given. Needle biopsy of the liver was repeated immediately to determine whether or not the tuberculous hepatitis had worsened. Microscopic sections showed a healed tubercle and hepatitis (figure 7); the evidence of sickle-cell disease described in the two preceding biopsy specimens was again noted (figures 4 and 5).

At the time of the third biopsy, quantitative urobilinogen studies were repeated. The amount of urine urobilinogen had increased to 253 mg. in twenty-four hours and the amount of fecal urobilinogen had increased to 456 mg. in twenty-four hours, the only abnormally high value for that determination throughout the patient's illness. The degree of sickling rose abruptly to 100 per cent; the erythrocyte sedimentation rate remained between 16 and 19 mm. per hour.

So far the patient had not developed symptoms which reflected the abrupt changes in laboratory findings. Within two days, however, he began having malaise and severe anorexia, followed shortly thereafter by nausea and vomiting. Abdominal pain began four days later. At first localized in the epigastric region, it radiated into the chest and simulated the pain of pulmonary infarction; however, a roentgenogram of the chest did not support that clinical impression, nor did the subsequent course of events.

The patient next entered into an episode of severe liver failure which did not respond to intensive therapy. Total serum bilirubin increased rapidly to 70 mg. per 100 ml. and


LIVER BIOPSY
LIVER BIOPSY
LIVER BIOPSY
BODY TEMPERATURE (ORAL) (°C and °F)
ESSENTIALLY NORMAL
BODY WEIGHT (KG)
OPTIMUM
NIGHT SWEATS
WEARINESS
MALAISE
COUGH
ANOREXIA
NAUSEA, VOMITING
ABDOMINAL PAIN
HEPATOMEGALY
GAMMA GLOBULIN (ZINC SO4 UNITS)
SERUM ALBUMIN GM %
SERUM GLOBULIN GM %
PATIENT EATING
THYMOL TURBIDITY (UNITS)
LIPID TURBIDITY MG %
BROMSULPHALEIN RETENTION (%AT 45 MINS)
CEPHALIN FLOCCULATION
BLOOD TRANSFUSION (● =500CC)
PENICILLIN (MILLION UNITS/DAY)
STREPTOMYCIN (GMS/DAY)
PARA AMINOSALICYLATE (GMS/DAY)
WEEKS
PATIENT J.F.
VARIOLA 25954

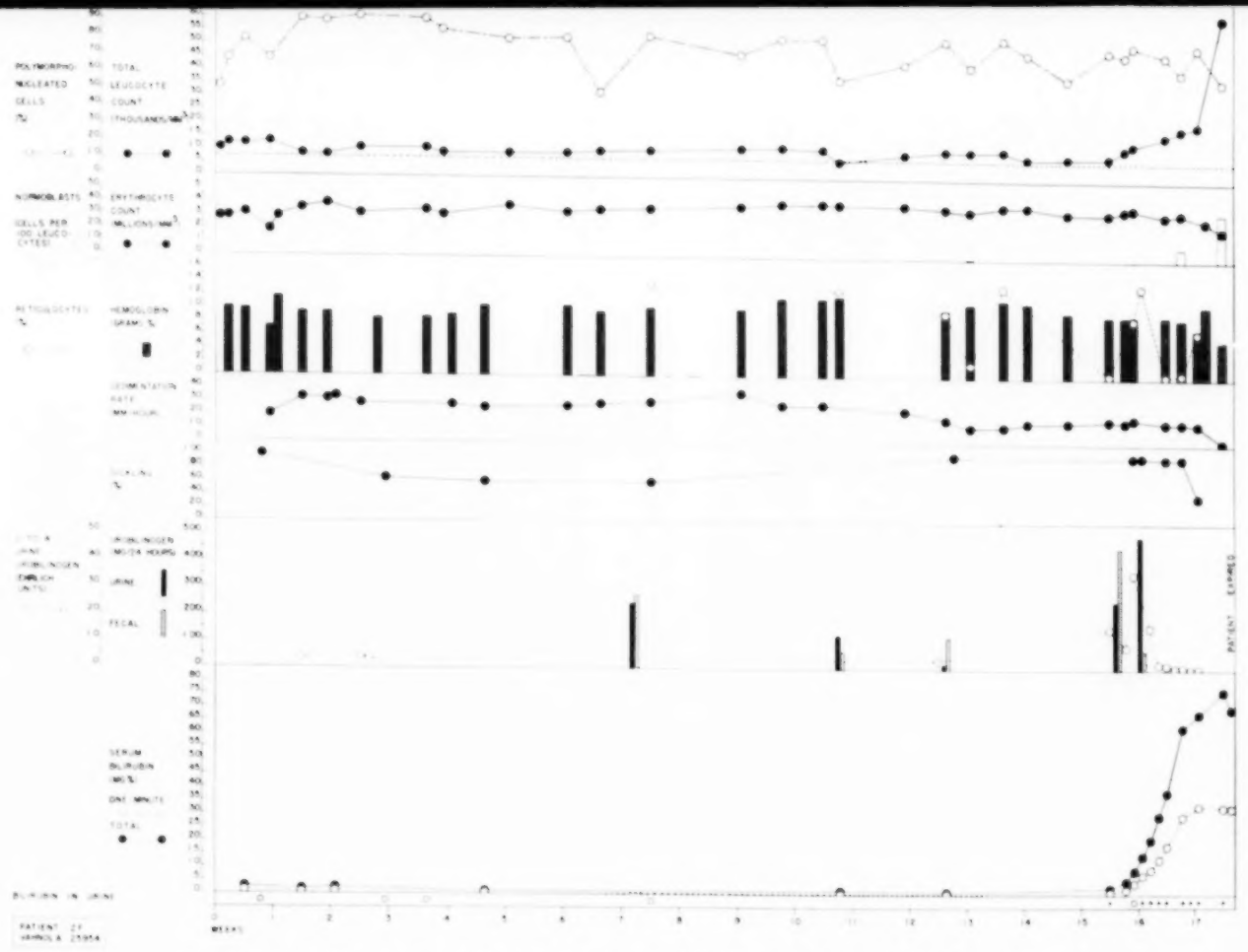


FIG. 2. Relationship of hematologic findings to serum bilirubin and fecal and urine urobilinogen.

one-minute bilirubin, to 32.8 mg. per 100 ml. The last quantitative determination of urine urobilinogen revealed the tremendous value of 504 mg. in twenty-four hours. At the same

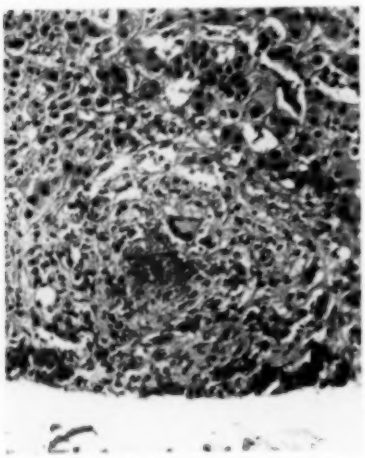


FIG. 3. Initial specimen obtained on eighth day of treatment with streptomycin and para-aminosalicylate. A caseous granuloma with Langhans' giant cell is shown.

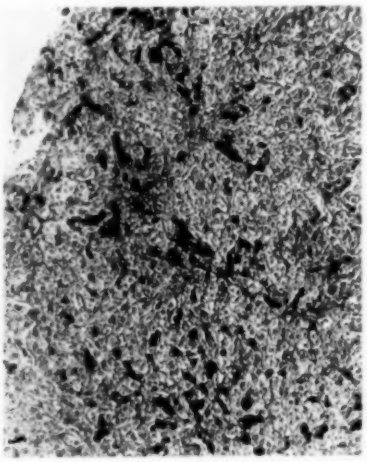


FIG. 4. Low-power view of initial biopsy specimen. Black areas represent sinusoids packed with erythrocytes, many of which are sickled (Masson's stain).

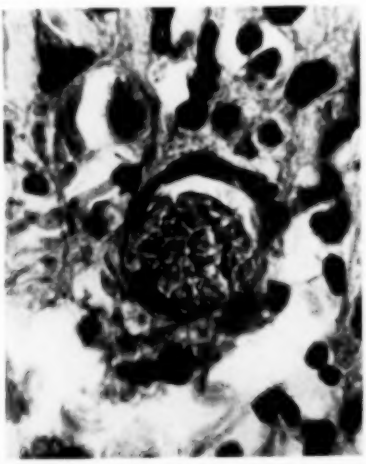


FIG. 5. Oil-immersion view demonstrating erythrophagocytosis by Kupffer cell

time, however, the amount of fecal urobilinogen was found to have decreased to 60 mg. in twenty-four hours. Subsequently, a rapid decrease in the amount of urine urobilinogen likewise occurred; specifically, values for the determinations of 2 to 4 p.m. excretion fell

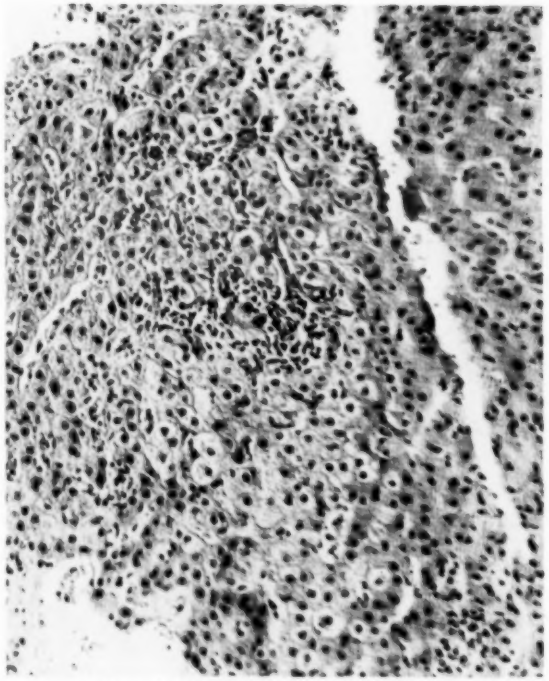


FIG. 6. Second biopsy specimen obtained on the forty-eighth day of treatment. A small, nonspecific granuloma is shown.

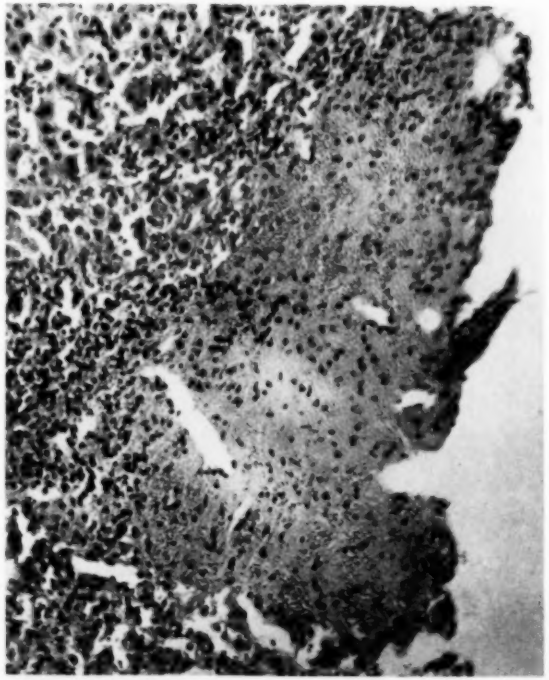


FIG. 7. Third biopsy specimen obtained on the one hundred and third day of treatment and at the onset of fatal post-transfusion hepatitis. A healed tubercle is shown and there is some evidence of hepatitis.

from 36 to 2.0 Ehrlich units within three days. Bilirubin appeared in the urine for the first time during the patient's illness. The total leukocyte count rose to 63,150 per cu. mm., but closer examination revealed that 36 per cent of the "leukocytes" were actually normoblasts. The sedimentation rate fell precipitously to 2 mm. per hour and there was a sharp decrease in the percentage of sickling. During this period the patient again began having a spiking fever, and he developed excruciating low back pain. He became oliguric and acidotic, then began passing blood in his urine and feces. Transfusions of whole blood were given because of increasing anemia. Finally, the patient lapsed into coma and died in a state of shock on the one hundred and sixteenth day of treatment and thirteen days after the onset of the terminal illness.

Autopsy Findings

Liver: The weight of the liver was 2,100 gm. The organ was quite firm in consistency. The capsule was smooth and showed some thickening about the gallbladder. Scattered grayish nodules were visible; they varied in diameter from 1 to 2 mm. Lobular structure was prominent. Microscopic examination revealed the capsule to be of normal thickness. Here and there in the portal spaces were seen irregular areas which were hyalinized and surrounded by a few lymphocytes; no definite tubercles were seen. In other portal spaces, increased infiltration by mononuclear cells and a few polymorphonuclear leukocytes were present. Some of these inflammatory cells were present as foci within the lobules in various sections. Some liver cells had undergone necrosis, and in these sites a few inflammatory cells were seen. The sinusoids were engorged with conglutinated erythrocytes, nearly all of which were sickled.

Spleen: The spleen weighed 110 gm. The capsule was thickened and grayish-white. Cut section revealed considerable scarring throughout the organ, which was firm in consistency. The splenic artery and vein were patent. Microscopic examination confirmed marked thickening of the capsule and trabeculae. Within the latter were seen dark structures presumed to be iron pigment bodies. The white matter was completely absent; the red pulp was filled with sickle cells. Iron pigment bodies were also present around and within walls of numerous blood vessels in the organ.

Lungs: Microscopic examination of the lungs showed alternating areas of atelectasis and emphysema. There was moderate interstitial fibrosis, which was focally placed. There were scattered large caseous areas surrounded by epithelioid cells with occasional Langhans' giant cells in the periphery. Sickle cells were seen within the capillary bed, but the percentage of sickling was not as high as it was in the liver. In other areas there was dense scarring involving alveolar spaces, and focal collections of lymphocytes were seen. Endothelial proliferation in arteries was noted. Within the alveolar spaces were found many large phagocytes filled with brown pigment. Small foci resembling infarcts were seen in which the alveolar spaces were stuffed with erythrocytes, a few of which were sickled.

Kidneys: The kidneys weighed 210 and 190 gm. Microscopic examination showed large glomeruli whose capillaries were filled with sickle cells. The convoluted tubules were lined by swollen granular cells. The loops of Henle and the collecting tubules contained bilirubin casts. Many tubules had pigment within the lining epithelial cells.

Bone marrow: Necrosis of the bone marrow was evident. Some small blood vessels were filled with sickle cells which appeared to be agglutinated. The general appearance was that of infarction of bone marrow.

The remaining autopsy findings added further evidence of sickle cell disease but otherwise did not contribute to the essence of this report.

COMMENT

Tuberculosis is a frequent cause of death in persons with sickle-cell anemia (6), so the simultaneous occurrence of the two diseases in this patient was not altogether surprising. Cultures of liver tissue obtained through serial biopsies and at autopsy were not successful

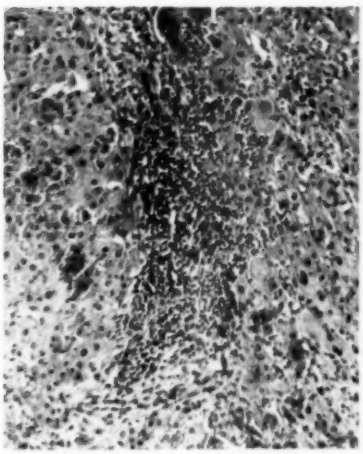


FIG. 8. Autopsy section of the liver showing an area of hepatitis considered post-transfusion in origin.

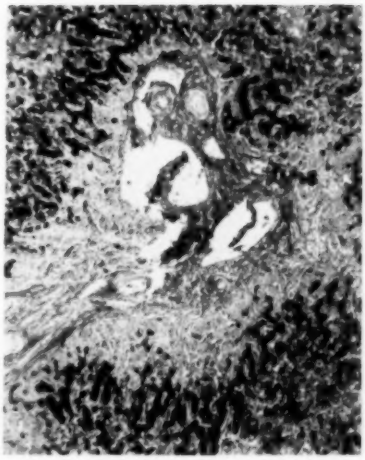


FIG. 9. Low power view of autopsy section showing marked engorgement of sinusoids with erythrocytes, many of which are sickled.

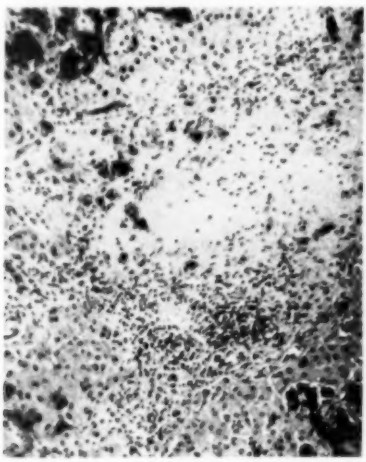


FIG. 10. Autopsy section showing a healed tubercle, hepatitis, and engorgement of sinusoids with erythrocytes.

in growing *Mycobacterium tuberculosis*; however, the diagnosis of hepatic tuberculosis was considered justified by the following facts:

> A typical tubercle was demonstrated in the initial biopsy specimen. There was an excellent response to treatment with streptomycin and PAS. The finding of pulmonary tuberculosis at autopsy made hepatic involvement in a miliary

process feasible. Positive cultures were not likely since all tissue specimens were obtained after antibiotic therapy had been instituted.

Furthermore, the liver appears to have a high degree of organ resistance to *Mycobacterium tuberculosis* (7) which may be contributed to, in part, by the attenuating effect of bile on that organism (8).

The clinical course of this patient, together with the evidence of tissue response demonstrated in serial biopsies of the liver, indicates that the occurrence of hepatic tuberculosis need not be of hopeless prognostic import; rather, remarkable improvement may result from treatment with streptomycin and PAS.

It is difficult to establish with a satisfying degree of certainty the diagnosis of post-transfusion hepatitis in a person with sickle-cell anemia, for the two diseases may cause identical symptoms, disturbances in laboratory tests, and histologic changes within the liver. In this patient it was thought that post-transfusion hepatitis developed in an organ previously damaged by miliary tuberculosis and showing the effects of smoldering sickle-cell disease. Following the onset of hepatitis, a sickle-cell crisis was precipitated and the combination of the two catastrophies resulted in fatal liver failure.

Evidence of that sequence of events, which is unescapably equivocal, is shown graphically in figures 1 and 2 and is summarized as follows: Onset of the classical signs and symptoms of viral hepatitis occurred 103 days following blood transfusion; the interval agrees with the incubation period of post-transfusion hepatitis. However, the signs and symptoms usually associated with a sickle-cell crisis did not occur until several days thereafter. Early in the course of the terminal illness, results of urobilinogen studies favored a process predominantly damaging to hepatic parenchyma (hepatitis) rather than a predominantly hemolytic process (sickle-cell crisis). As the illness fulminated, eventual reduction in both urine urobilinogen and fecal urobilinogen was compatible with cholangiolar damage which could have been caused by hepatitis and/or sickle-cell crisis (9). That was also true of the hematologic changes which occurred a short time before the patient died. The third liver biopsy (figure 7), performed at the onset of the terminal illness, revealed hepatitis but did not show significant increase in the evidence of sickle-cell disease. However, autopsy sections of the liver obtained thirteen days later (figures 8, 9, and 10) revealed, not only severe hepatitis, but also marked increase in the evidence of sickle-cell disease. Furthermore, the percentage of sickled erythrocytes was much higher in the vascular spaces of the liver than it was in other organs, indicating that a local crisis had been precipitated in an organ which had become the site of intercurrent infection.

This case prompts the suggestion that post-transfusion hepatitis, masquerading as a sickle-cell crisis, may, more often than is recognized, be the cause of death in persons with sickle-cell anemia, a disease which in its course necessitates repeated blood transfusions. Thus, one explanation is ventured for the not infrequent finding of post-necrotic cirrhosis at autopsies of victims of sickle-cell anemia. The present writer has recently been informed of two such cases (10).

SUMMARY

A case of hepatic tuberculosis in a 32-year-old Negro male with sickle-cell anemia is presented. After improving remarkably upon treatment with streptomycin and sodium para-aminosalicylate, the patient died in liver failure attributed to post-transfusion hepatitis which precipitated a sickle-cell crisis. Photomicrographs of serial needle biopsies and autopsy sections of the liver which demonstrate the three disease processes are shown.

SUMARIO

Tuberculosis Hepática en un Enfermo con Drepanocitemia y con Terminación en Hepatitis Posttransfusional Letal

Preséntase un caso de tuberculosis hepática en un negro de 32 años que padecía de drepanocitemia. Después de mejorar notablemente al ser tratado con estreptomicina y para-aminosalicilato sódico, el enfermo falleció de insuficiencia hepática imputada a una hepatitis consecutiva a la transfusión, que precipitó una crisis drepanocitaria. Preséntanse microfotografías de biopsias seriadas con agujas y cortes autópsicos del hígado que muestran los tres procesos patológicos.

RESUME

Tuberculose hépatique chez un malade atteint d'anémie falciforme dont l'issue a été une hépatite fatale post-transfusionnelle

Présentation d'un cas d'hépatite tuberculeuse chez un nègre, âgé de 32 ans, atteint d'anémie faliciforme. Après une amélioration remarquable consécutive au traitement par la streptomycine et le para-aminosalicylate de sodium, le malade a succombé à une hépatite post-transfusionnelle qui a précipité une phase de production de cellules falciformes. Présentation de microphotographies en série de biopsies et de prélèvements post mortem de tissu hépatique, où les trois processus sont visibles.

Acknowledgment

Gratitude is expressed to Dr. Joseph Ziskind for his interpretations of tissue preparations; to Dr. Kurt Sachs for his assistance in performance of biopsies; and to Mrs. Shirley Fairchild, M. T., for the technical assistance. Photographic work was done by Mr. F. W. Busie and Mr. W. D. Bohon.

REFERENCES

(1) Craddock, C. G., and Meredith, H. C., Jr.: Punch liver biopsy in the diagnosis of miliary tuberculosis: Report of a case, New England J. Med., 1949, *241*, 527.
(2) Janbon, M., Cazal, P., and Bertrand, L.: Liver puncture biopsy in miliary tuberculosis, Presse méd., 1949, *57*, 854.
(3) Mansuy, M., and Seifferth, W. J.: Miliary tuberculosis of the liver; liver biopsy as an adjunct to diagnosis, Am. J. M. Sc., 1950, *220*, 206.
(4) Cohen, A. G., and Giges, B.: Punch biopsy of liver in detection of hematogenous tuberculosis, J.A.M.A., 1951, *146*, 1416.
(5) Christian, E. R.: An evaluation of needle biopsy of the liver, Am. J. Med. (in press).
(6) Margolies, P. M.: Sickle cell anemia, Medicine, 1951, *30*, 357.
(7) Rich, A. R.: The Pathogenesis of Tuberculosis, Charles C Thomas, Springfield, Illinois, 1944.
(8) Lichtman, S. S.: Diseases of the Liver, ed. 2, Lea and Febiger, Philadelphia, 1949.
(9) Henderson, A. B.: Sickle cell anemia, Am. J. Med., 1950, *9*, 757.
(10) Pizzolato, P.: Personal communication.

Notes

PROTHROMBIN TIME DURING PARA-AMINOSALICYLIC ACID THERAPY

Two Thousand Determinations in 400 Patients

Opinions differ on the tendency to hemorrhage and especially on the prothrombin time during medication with para-aminosalicylic acid (PAS). Profuse hemorrhage and marked decrease in the prothrombin index have been described by some investigators.[1, 2] Others report that they have seldom or never seen more than an insignificant decrease in the prothrombin index, and that an increase of clinical importance in the tendency to hemorrhage during such medication is rare.[3-11]

As some of these reports have been cited incorrectly by later writers [12, 13] without any convincing material of their own, they have favored the spread of the opinion that medication with PAS may lead to significant hemorrhagenic phenomena.

In an endeavor to clear up this point, the present writers studied the prothrombin time before and during PAS therapy in a series of 400 unselected patients.

The series, which consisted of practically all of the patients who were treated at the sanatorium in the course of a five-month period, also included advanced cases of pulmonary tuberculosis and patients with serious complications such as anemia, uremia, and diabetes. The diet was mixed and rich in calories, proteins, and vitamins. Some of the patients received a special diet because of complicating diseases. None of them received supplementary vitamin K. Ninety-five per cent of the patients had tuberculosis of various localizations and severity; the remaining 5 per cent showed no signs of tuberculosis.

The prothrombin index was determined by the micromethod of Quick-Lehmann,[15] normal values lying between 80 and 120. In those cases in which the prothrombin index was measured on several occasions before medication with PAS was started, the means of these values were taken as the initial value. The values recorded during every one-

[1] Croizat, P., Favre-Gilly, J., Creyssel, R., and Milhet, M. G.: Lyon méd., 1950, *183*, 349.

[2] Ducourt, A., Ollagnier, C., Touraine, R., and Caglinger, H.: Lyon méd., 1950, *183*, 288.

[3] Bavin, E. M.: J. Pharm. & Pharmacol., London, 1949, *1*, 700.

[4] Gordin, R., Nordstrom, K., and Riska, N.: Tr. of the XVI Scandinavian Congress for Tuberculosis in Oslo, May 29-31, 1952.

[5] Kristensson, A.: Acta tubere. Scandinav., 1951, *25*, 182.

[6] Kristensson, A.: Tr. of the XVI Scandinavian Congress for Tuberculosis in Oslo, May 29-31, 1952.

[7] Lundberg, S.: Nord. med., 1951, *45*, 745.

[8] Lynch, M. J. G.: J. Clin. Path., 1950, *4*, 114.

[9] Madigan, D. G., Griffith, L. L., Lynch, M. J. G., Bruce, R. A., Kay, S., and Brownlee, G.: Lancet, 1950, *1*, 239.

[10] Secousse, H., Tessier, R., Secousse, J. P., and Pène, P.: Rev. de la tubere., 1950, *14*, 744.

[11] Soragni, E., Rezza, E., and Gheradini, A.: Acta paediat. latina, 1950, *3*, 50.

[12] Forsgren, E.: Svenska läk. tidn., 1950, *47*, 3024.

[13] Forsgren, E.: Svenska läk. tidn., 1951, *48*, 880.

[14] Morandi, L., Ochsner, H., and Neuenschwander, A.: Schweiz. med. Wchnschr., 1951, *81*, 1301.

[15] Lehmann, J.: Nord. med., 1941, *12*, 3192.

month period were also treated in this way. The table is based on 800 such means representing some 2,000 determinations made on various days.

Granulated PAS (Ferrosan) was given, sometimes in the form of the acid and sometimes in the form of sodium and calcium salts. Every patient received approximately 0.2 gm. per kg. of body weight per day.

If the administration of PAS was suspended for periods of less than one month at a time, medication was said to be uninterrupted. Prothrombin values recorded during such suspension, however, were not included in the calculation of the means.

Most of the patients also received short courses of treatment with other antimicrobial agents.

Para-aminosalicylic acid therapy was also usually continued during and after surgical intervention as well as during spontaneous hemorrhage, such as hemoptysis, uterine bleeding, and hematuria. Prothrombin determinations made during intercurrent diseases were included in the calculation of the means.

The results are summarized in the table.

TABLE 1

PROTHROMBIN INDEX DETERMINED IN 400 SANATORIUM PATIENTS BEFORE AND DURING PAS THERAPY

DURATION OF PAS THERAPY	NUMBER OF PATIENTS		AVERAGE PROTHROMBIN INDEX	PERCENTAGE OF PATIENTS WITH INDEX <80
	Examined	Prothrombin Index <80		
0	275	13	97	4.7
months				
Up to 1	130	7	96	5.4
1–2	109	7	93	6.4
2–3	88	4	96	4.5
3–4	54	3	95	5.5
4–5	44	2	96	4.8
5–6	37	0	95	0.0
6–12	64	2	94	3.1
Total during PAS therapy	526	25	95	4.8

The table shows the prothrombin index determined in 400 patients: 275 determinations were made before the institution of PAS therapy and 526 after the administration of PAS for a period up to one year.

The average monthly prothrombin indices were somewhat below the normal average level throughout. This can be explained by the fact that the series did not consist of normal persons.

A value of less than 80, the lower limit of the normal range, was recorded in 4.7 per cent before and in 4.8 per cent during PAS therapy; thus, practically no difference was found. Neither was any appreciable difference found between the monthly percentages. None of the pathologic values recorded were below 60, and no fewer than 30 of the 38 pathologic determinations lay between 71 and 79.

Simultaneous clinical observation revealed no evidence suggestive of increased hemorrhagic tendency in connection with PAS therapy, not even during or after operation.

Neither was any increase observed in the tendency to hemoptysis, metrorrhagia, menorrhagia, hematuria, or intestinal bleeding during medication with PAS. Medication with PAS was not postponed or suspended because of hemorrhage.

The investigation thus showed that the administration of PAS in a dose of approximately 0.2 gm. per kg. of body weight per day for a period up to one year, with suspension in the event of disorders of the digestive tract (diarrhea, nausea, vomiting), had no appreciable depressant effect on the prothrombin index. Neither were any clinical observations made which might suggest an increase in the hemorrhagic tendency during treatment with PAS.

The present study cannot explain the disagreement between earlier research workers in this field. It may, however, be ascribed to differences between the PAS preparations used; to differences in the composition of the diets, the most remarkable cases of hemorrhage being reported from the south of France; to differences in dosage and schemes of medication, such as suspension during diarrhea; and to allergic reactions.

In summary: The prothrombin index was determined in 400 patients before and during para-aminosalicylic acid (PAS) therapy, which was usually continued during operative procedures or episodes of spontaneous hemorrhage. The administration of the drug in a dose of approximately 0.2 gm. per kg. of body weight for a period up to one year, with temporary cessation during any intestinal disorder, was not accompanied by an appreciable prolongation of the prothrombin time. Neither did any clinical observations suggest that PAS therapy is attended by an increased tendency to hemorrhage.

Sollidens Sanatorium
Östersund, Sweden

Lembit Norviit
Bo Carstensen

September 9, 1952

SENSITIVITY OF ACTINOMYCETALES TO ISONICOTINIC ACID HYDRAZIDE, COMPARED TO OTHER SYNTHETIC AND ANTIBIOTIC ANTITUBERCULOSIS AGENTS[1]

The systematic position of the *Actinomycetales* has caused greater confusion than has that of many of the other groups of microorganisms. There have been many speculations on the relationships of *Actinomycetes* to the true bacteria and fungi. This was particularly true of the relationship of the genera *Streptomyces*, *Nocardia*, and *Micromonospora* to the fungi, and of the *Nocardia* and *Mycobacterium* to the true bacteria.[2]

As new reagents which act selectively upon different groups of microorganisms are discovered, they become of particular interest because of the possibility of their throwing light on the aforementioned relations. The introduction of antibiotics and some of the synthetic compounds which act selectively upon the *Mycobacteria*, the true bacteria, the *Actinomycetes*, and the fungi made possible a new approach to the elucidation of this problem.

Actinomycetes, as a group, are known to be sensitive to those antibiotics which are primarily antibacterial in nature, such as penicillin and streptomycin, and are resistant to the antifungal antibiotics, such as actidione, fradicin, fungicidin, and candicidin.[3, 4, 5] This fact contributes evidence that the actinomycetes are more closely related to the bacteria than to the fungi. Para-aminosalicylic acid (PAS) and isonicotinic acid hydrazide (isoniazid) are known to have mainly antimycobacterial activity.[6, 7, 8, 9] A comparison of the activity of these compounds, on a large number of *Actinomycetales*, with that of two antibiotics (streptomycin and neomycin) which possess marked antimycobacterial properties is, therefore, of interest.

Since isoniazid is a synthetic tuberculostatic agent, the activity of which has only recently been recognized, a preliminary survey of its selective antimicrobial activity was first carried out. The serial dilution method was used on a solid peptone-glucose medium.[10] At a level of 1,000 γ per ml., no growth inhibition was observed against a number of common bacteria, including *Escherichia coli*, *Shigella sonnei*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Staphylococcus aureus*, *Bacillus cereus*, and *B. subtilis*, and fungi, including *Rhizopus nigricans*, *Candida albicans*, *Ceratostomella ulmi*, *Saccharomyces cerevisiae*, *Trichoderma koeningi*, *Aspergillus niger*, *Penicillium notatum*, and *Alternaria* sp.

The activity of the four antituberculous agents was then determined against various

[1] Paper of the Journal Series, New Jersey Agricultural Experiment Station, Rutgers University—State University of New Jersey, Department of Microbiology.

[2] Waksman, S. A.: The *Actinomycetes*, Chronica Botanica Co., Waltham, 1950.

[3] Waksman, S. A., Katz, E., and Lechevalier, H.: J. Lab. & Clin. Med., 1950, *36*, 93.

[4] Lechevalier, H., Acker, R. F., Corke, C. T., Haenseler, C. M., and Waksman, S. A.: Candicidin, a new antifungal antibiotic, Mycologia (in press).

[5] Waksman, S. A., Romano, A. H., Lechevalier, H., and Raubitschek, F.: Bull. World Health Organization, 1952, *6*, 163.

[6] American Trudeau Society: Current status of isonicotinic acid hydrazide in the treatment of tuberculosis, Am. Rev. Tubere., 1952, *65*, 649.

[7] Lehman, G.: Svenska lak. tidn., 1946, *43*, 2029.

[8] Pansy, F., Stander, H., and Donovick, R.: Am. Rev. Tubere., 1952, *65*, 761.

[9] Sievers, O.: Svenska lak.-tidn., 1946, *43*, 2041.

[10] The medium consisted of 1 per cent glucose, 0.5 per cent peptone, 0.5 per cent NaCl, 0.3 per cent meat extract, 1.5 per cent agar, in tap water. The pH was adjusted to give 7.2 after sterilization.

Actinomycetes and *Mycobacteria*, including one *Actinomyces*, 26 *Streptomyces*, 27 *Nocardia*, 6 *Micromonospora*, 20 nonpathogenic strains of *Mycobacterium*, and 3 human and animal pathogens of the same genus. All the nonpathogenic *Actinomycetales* were tested by the plate dilution method described. The sensitivity of *A. boris* was determined in brain heart infusion agar in anaerobic Petri dishes. The sensitivity of the pathogenic *Mycobacteria* was measured in liquid media, the Squibb modification of Kirchner's synthetic medium being used.

As a group, all the *Actinomycetales* tested, except one *Nocardia*, two *Streptomyces*, and the *Actinomyces*, were sensitive to less than 10 γ of streptomycin and neomycin per ml.

TABLE 1

SENSITIVITY OF DIFFERENT ACTINOMYCETES AND MYCOBACTERIA TO ISONIAZID

TEST ORGANISM	ISONIAZID REQUIRED FOR COMPLETE INHIBITION OF GROWTH
	γ *per ml.*
Mycobacterium tuberculosis, human, H37Rv	0.01
M. tuberculosis, human, H37RvR*	0.05
M. tuberculosis, bovine	0.05
M. tuberculosis, avian	>0.50
Mycobacterium phlei (4 strains)	<5–10
M. phlei (1 strain)	>1,000
M. smegmatis (5 strains)	<5–10
M. fortuitus	<5
M. lacticola	100
Mycobacterium sp. (6 strains)	<5–5
Mycobacterium sp. (4 strains)	100–200
Actinomyces boris	>100
Micromonospora sp. (6 strains)	10–100
Nocardia sp. (6 strains)	10–80
Nocardia sp. (9 strains)	100–500
Nocardia sp. (11 strains)	750–>1,000
Streptomyces (2 strains)	100
Streptomyces (24 strains)	750–>1,000

* Streptomycin-resistant.

PAS is active against pathogenic *Mycobacteria* in a concentration of approximately 1.6 γ per ml.;[8] bacteria are resistant to the action of this compound and require a concentration of 1.25 to 2.5 per cent for inhibition.[9] In the present tests, all the nonpathogenic *Actinomycetales* were inhibited by an intermediate concentration of 350 to 750 γ of PAS per ml.

From the phylogenic point of view, the behavior of the *Actinomycetales* toward isoniazid is of interest (table 1).

The susceptibility of the various *Actinomycetales* to isoniazid tended to follow their phylogenic position: the pathogenic members of the genus *Mycobacterium* were susceptible to less than 1 γ per ml., the avian form being least susceptible. The saprophytic forms of *Mycobacterium* were, as a rule, less susceptible, certain forms being resistant to 100

and even 1,000 γ per ml.; most of them were, however, susceptible to less than 5 and 10 γ per ml. The *Micromonospora* were as a group more resistant than the *Mycobacteria* (10 to 100 γ per ml.). The *Nocardia* were also moderately more resistant, most of them requiring 80 to 300 γ per ml. for growth inhibition; some were more susceptible (10 γ per ml.), and others were resistant (more than 1,000 γ per ml.). The *Streptomyces*

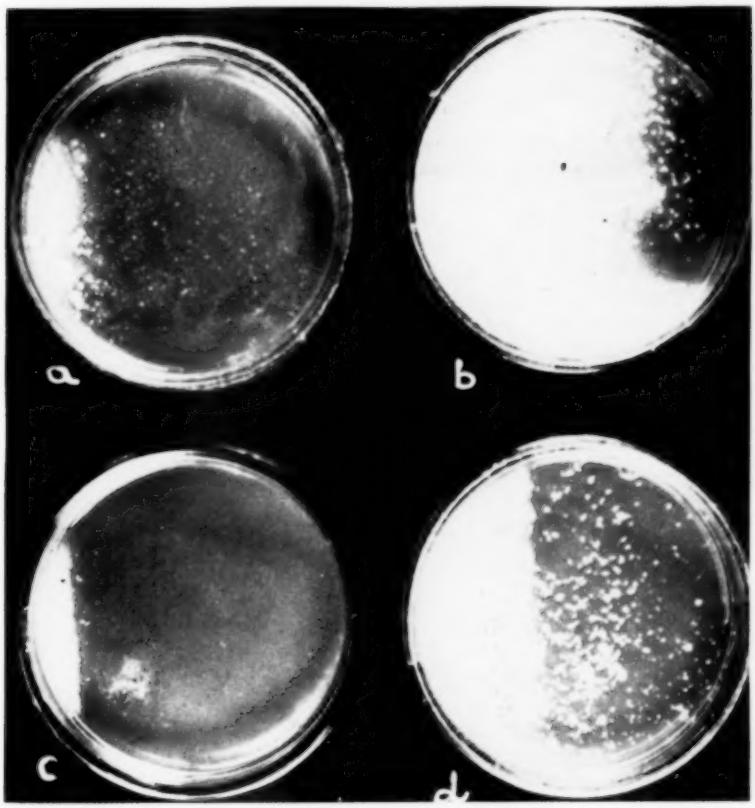


FIG. 1. Effect of four antituberculous agents on *Mycobacterium smegmatis*. Szybalski's gradient plate: *a*, streptomycin, 0.5 to 5 γ per ml.; *b*, PAS, 1 to 1,000 γ per ml.; *c*, neomycin, 0.5 to 5 γ per ml.; *d*, isoniazid, 0.5 to 5 γ per ml.

were more resistant, requiring as a rule more than 1,000 γ per ml. The various genera of the *Actinomycetales* can thus be listed in the following order of increasing resistance to isoniazid.

Pathogenic *Mycobacteria* → saprophytic *Mycobacteria* → *Micromonospora* → *Nocardia* → *Streptomyces*.

In the study of any new antimicrobial agent, the question always arises to what extent such a reagent will facilitate the development of resistance among susceptible

organisms. To throw some light on this question bearing upon the different antituberculosis agents, a comparison was made of their action upon *M. smegmatis*, using the Szybalski gradient plate method,[1] with peptone-glucose agar medium. Cells resistant to isoniazid were abundant in the *M. smegmatis* population, 25 isoniazid-resistant colonies being isolated from plates containing 10 and 25 γ of isoniazid per ml.; none of the strains was resistant to 70 γ per ml. (figure 1). Fewer strains appeared to be resistant to streptomycin and only very few to neomycin.

The data presented here permit the following conclusions:

In some of their metabolic reactions, the *Actinomycetales* are more closely related to the bacteria than to the fungi since, as a rule, they are susceptible to antibacterial antibiotics and resistant to antifungal antibiotics.

The *Streptomyces* might be more closely related to the *Eubacteriales* than their morphology suggests since they are, as a rule, very resistant to the action of isoniazid. The same data suggest that the *Mycobacteria*, which are very susceptible to isoniazid, might be, in some of their metabolic reactions at least, farther away from the true bacteria than are the other *Actinomycetales*, in spite of their morphologic similarity.

The members of the genera *Streptomyces* and *Micromonospora* showed a fair amount of homogeneity in their sensitivity to isoniazid. Large differences in susceptibility were observed among the members of the genus *Mycobacterium* and even more among the members of the genus *Nocardia*. This is but another indication that the classification of the latter two genera still requires considerable attention. It should be remembered that the genus *Nocardia* is most likely an artificial intermediate group which might contain a fair number of atypical *Streptomyces* and *Mycobacteria*. There was no correlation, however, between the resistance to isoniazid and morphologic characteristics. Some strains of *Nocardia* resembling those of *Streptomyces* in the formation of aerial hyphae were susceptible to isoniazid, and some with colonies like those of *Mycobacteria* were resistant.

When studied *in vitro*, a large number of cells of *M. smegmatis* readily became resistant to intermediate concentrations of isoniazid, whereas the development of resistance to neomycin was very infrequent. The development of resistance to streptomycin fell between these two.

Acknowledgment

The authors are indebted to Dr. R. E. Gordon for furnishing the various cultures used in these tests and to Mr. F. Gregory for making the sensitivity tests of the pathogenic *Mycobacteria*.

Department of Microbiology
Rutgers University
New Brunswick, New Jersey

Selman A. Waksman
Hubert A. Lechevalier

October 22, 1952

[1] Szybalski, W.: Bact. Proc., 1952, p. 36.

THE NATURE OF THE VIRULENCE OF HUMAN AND BOVINE TYPES OF TUBERCLE BACILLI FOR THE RABBIT

Twenty-four years ago,[1] in an effort to determine the cause of the much greater susceptibility of the rabbit to the bovine as distinguished from the human-type tubercle bacillus, parallel groups of rabbits were injected intravenously with equal amounts of both types of bacilli. At different intervals after infection, the various organs of both groups were quantitatively cultured and the resulting colonies were enumerated. It was found that the number of colonies recovered from the several organs of the rabbit during the first two weeks after infection with human bacilli greatly exceeded those recovered from the same weights of the same organs of rabbits infected with bovine bacilli. Furthermore, this initial greater recovery of tubercle bacilli of the human type was followed by a more rapid sterilization of their organs than occurred in rabbits infected with bovine bacilli.

These observations led to the concept that the greater resistance of the rabbit to the human bacillus was a result of the apparently more rapid initial growth of this microorganism in the tissues of the animal. This conclusion seemed to rest on the general biologic law that the greater the stimulus the quicker and more intense the response. Since there was inherent evidence that even the bovine bacillus is destroyed in the liver, spleen, and bone marrow after a preliminary multiplication, it appeared probable that the immunity of these organs is acquired during the course of the infection as a result of the stimulation of the body defenses by exposure to the accumulated antigen. Furthermore, it is well known that the rapidity and intensity of development of increased resistance to the tubercle bacillus is a function of the number of bacilli used in immunization. Again, in the study in question it was demonstrated that the organs which destroy the bovine bacillus during the course of the infection do so more rapidly if the infection dose is large than if it is small. All of these considerations seemed to point to the possibility that the virulence of a tubercle bacillus for the rabbit is inversely proportional to its initial rate of growth. The apparently slow and insidious rate of initial multiplication of the bovine bacillus in the rabbit seemed to stimulate acquired resistance more slowly than the apparently more rapid initial multiplication of the human bacillus in this species.

In 1944, Dr. Arnold R. Rich in his *Pathogenesis of Tuberculosis*[2] analyzed these data and did not accept the interpretation placed on them. In the review of this book by the present writer[3], it was admitted that the relative virulence of bovine and human types of tubercle bacilli for the rabbit could not be explained on the above hypothesis. In the 1951 edition of the same volume, Rich has again keenly dissected the evidence and pointed out that, while it could not be denied that more human-type bacilli were recovered from the rabbit infected with human-type tubercle bacilli early in the course of the disease than occurs with bovine bacilli, this difference was not due to the actual greater numbers of viable human-type bacilli present in the rabbit's organs at that time but to the greater ease with which human-type bacilli could be recovered from the tissues than is true for bovine bacilli. Indeed, he pointed out that if, instead of considering the total numbers of bacilli recovered at different intervals from the different organs of rabbits infected with these two types of bacilli, their respective relative rates of increase over the initial deposition in the various organs is studied, it was actually demonstrated in this

[1] LURIE, M. B.: J. Exper. Med., 1928, *48*, 155.

[2] RICH, A. R.: The Pathogenesis of Tuberculosis, Charles C Thomas, Springfield, Illinois, 1944.

[3] LURIE, M. B.: *The Pathogenesis of Tuberculosis* by ARNOLD R. RICH (book review), Science, 1944, *100*, 407.

same study that the rate of growth of the bovine bacilli in the organs of rabbits is greater than that of the human bacilli. On re-examination of these data by the present writer, it is clear that the original interpretation was erroneous and the concept must be retracted. It is plain, however, that the actual observations made, if properly interpreted, would have resulted in a correct conclusion.

It is important to emphasize in this relation that, while the cultural methods used did not yield accurate information on the absolute number of viable tubercle bacilli present in a given sample of tissue, they did give reliable information on the relative numbers present. That this is true has recently been forcefully demonstrated to the writer's mind in the observed constant relationship which was found to hold between the number of virulent bovine tubercle bacilli cultured from the air and the number of grossly visible tubercles generated in rabbits inhaling it. Thus, in twenty-six experiments, a constant number of 3.3 $\pm$ 1.4 bacillary units was required to generate one tubercle. It is clear that both variables must have been quantitatively determined. Both the bacilli inhaled as enumerated by culture of the respired air and the number of tubercles found were either the actual numbers involved or multiples of them. Otherwise, no constant relationship could obtain between them.[4]

That the virulence of a tubercle bacillus for a given host is not inversely related to its initial rate of growth in the body is apparent from more recent studies by the present writer on the nature of resistance to tuberculosis. This is revealed by the response of natively susceptible and natively resistant rabbits to the quantitative inhalation of human-type tubercle bacilli.[5, 6] If it were true that the greater resistance of rabbits to human-type than to bovine-type tubercle bacilli is due to the more rapid initial multiplication of the former and their consequent more rapid destruction, it would follow that in natively more resistant rabbits or organs the initial growth of the bacilli, i.e., the stimulus to acquire resistance, should be greater. But the contrary was found to be true. Indeed, in the paper published in 1928, it was shown that the organs which restrict the initial growth of bacilli to the greatest degree develop immunity faster and more completely than the natively more susceptible organs. Likewise, it has been conclusively shown that the macrophages of natively resistant rabbits restrict the initial multiplication of inhaled human-type tubercle bacilli much more than do the macrophages of the natively susceptible animal.

Thus, it can be said of both organ and species resistance that the greater the initial retardation of multiplication, the more rapid and complete is the destruction of the microorganism which results from the acquired immunity. As was done in 1928, the present writer again quotes an old maxim of Theobald Smith "acquired resistance is only a specific increment of natural resistance."

In the light of the above, it is concluded that the old inference that virulence is inversely proportional to the initial rate of growth of the bacilli in the body is no longer tenable.

Henry Phipps Institute
University of Pennsylvania
Philadelphia, Pennsylvania

Max B. Lurie

November 12, 1952

[4] Lurie, M. B., Heppleston, A. G., Abramson, S., and Swartz, I. B.: Am. Rev. Tuberc., 1950, *61*, 765.

[5] Lurie, M. B., Abramson, S., and Heppleston, A. G.: J. Exper. Med., 1952, *95*, 119.

[6] Lurie, M. B., Zappasodi, P., Dannenberg, A. M., Jr., and Weiss, G. H.: On the mechanism of genetic resistance to tuberculosis and its mode of inheritance, Am. J. Human Genetics (in press).

Correspondence

LUNG IMMOBILIZER THERAPY IN PULMONARY TUBERCULOSIS

To the Editor of the American Review of Tuberculosis:

Dr. Barach objects to our attributing the basic principle of the lung immobilizing chamber to Thunberg. However, in one of the references (9) Barach stated "the mechanism by which adequate pulmonary ventilation was provided, included use of the principle of alternating pressure described by Thunberg." Possibly a preferable choice of words on our part would have been "adapted" rather than "applied."

Dr. Barach objects that he did not recommend eight hours a day, nor two four-hour periods of treatment. However, in the reference cited (6), he gave three periods: two of four hours each, one of two and one-half, then said that favorably affected patients were treated from eight to eleven hours a day, implying that improvement was noted on an eight-hour schedule. Dr. Barach cites this same reference in his letter to illustrate how his papers had been "critically misrepresented."

Furthermore, in an outline "prepared for investigators who may be interested in our appraisal of the results of operation of the chamber," Barach and Eastlake stated: "However, whether or not eight hours a day is apt to produce as good a result as ten or eleven hours a day, which is employed in our cases, is something about which we cannot express a confident opinion. Dr. Bellis in Winnebago, Wisconsin, and Dr. O'Brien in Hadenville, Massachusetts, have had some excellent results on an eight-hour daily period in which arrest of disease followed this regime, and, also, in some patients without streptomycin and other therapy."

In a discussion of a paper (7), Bellis said that he used four-hour periods applying one or two a day as seen indicated, and mentioned his favorable results.

Dr. Barach objects to our maintaining the patient's activity. In other words, he wishes to impose strict bed rest and use the lung immobilizing chamber simultaneously. Our aim was to have but one variable—the immobilizing chamber; with a baseline of patient activity established, the effect of the chamber, if any, could then be observed.

We are entirely in agreement with Dr. Barach's observation that "their investigation was not designed to test the validity of immobilizing lung chamber therapy according to our regimen but for a scientific objective of their own." That objective was to determine whether or not the introduction of chamber therapy alone, under the conditions stated, had any influence upon the course of the disease in the patients studied.

Having attained that objective, we did not feel that the results were sufficiently promising to justify a similar study introducing longer periods of treatment or any other variant.

Dr. Roger Hemphill, the senior author, concurs in these remarks.

Veterans Administration Center
Wood, Wisconsin

John D. Steele
George C. Owen

November 6, 1952

American Trudeau Society

Medical Section of the National Tuberculosis Association

Resection of Residual Necrotic Lesions

A Report of the Committee on Therapy

Pulmonary tuberculosis treated by combined chemotherapy for prolonged periods, either alone or in association with temporary collapse therapy, often improves to such an extent that roentgenograms are stable, cavities are closed and sputum cultures are consistently negative for tubercle bacilli. Usually residual roentgenographic shadows persist, and it is generally agreed that most residual shadows represent necrotic lesions which have not resolved completely. Meticulous dissection of these necrotic lesions in surgical specimens often reveals bronchial communication and demonstrates that they are inspissated cavities with the morphologic prerequisites for potential relapse. From this point of view, the resection of residual necrotic lesions appears to be a logical therapeutic procedure.

Although the histopathology of these lesions suggests the possibility of relapse, recent bacteriologic studies have been interpreted as demonstrating that the majority of the bacilli in the residual necrotic lesion are dead. If this were true, the bacteriologic prerequisites for relapse would not be present and resection would be unnecessary. Unfortunately, laboratory techniques for the determination of viability are not sufficiently refined so that the problem can be considered solved. Until such time that incontrovertible evidence can be presented to support the view that the tubercle bacilli in these lesions are, in fact, dead, it would seem reasonable to resect such lesions in patients who are good surgical risks.

The size and location of residual lesions, the extent of cavitation at the start of prolonged chemotherapy, a history of relapse, and an estimate of host resistance will all influence the decision to resect. It should be emphasized, however, that the importance of these factors in favoring relapse after prolonged chemotherapy is not established.

There are undoubtedly situations and localities where facilities are limited and the resection of residual necrotic lesions cannot be carried out under ideal conditions. Here the patient would be better served if residual necrotic lesions were not resected.

David T. Carr
C. A. Castle
J. Maxwell Chamberlain
Nicholas D. D'Esopo
John B. O'Connor
Karl H. Pfuetze
Carl W. Tempel
William B. Tucker

Robert H. Ebert, *Chairman*

The Current Status of Isoniazid in the Treatment of Tuberculosis

A Report of the Committee on Therapy

A previous report of this committee[1] mentioned the use of isoniazid in the treatment of tuberculosis and called attention to the fact that isoniazid-resistant tubercle bacilli appeared rapidly when this drug was used alone. Subsequent studies have confirmed this observation. Other studies suggest that the emergence of isoniazid-resistant strains of tubercle bacilli may be prevented or delayed by the concurrent administration of streptomycin or *p*-aminosalicylic acid (PAS) or both. For these reasons, patients should not be treated with isoniazid alone. Further studies are needed to determine which combination of drugs will be most effective. In the meantime, if isoniazid is used, streptomycin or PAS or both should be given concurrently.

This committee is collecting reports of toxic reactions to isoniazid. Preliminary data emphasize the frequency of central nervous system effects, some of which are serious. The reactions vary from simple hyperreflexia to acute psychoses of the manic type. These reactions occur more frequently in patients with previous cerebral disease and idiopathic epilepsy. There is some experimental evidence that they might be prevented by the concurrent administration of phenobarbital. Allergic reactions have also been reported and may be manifested as dermatitis, chills and fever, purpura, arthralgia, or asthma. Albuminuria and microhematuria have been common, but not serious. Hepatic damage has been detected in only a few instances. No serious blood dyscrasia has yet been reported.

Iproniazid appears to be even more toxic than isoniazid and is still available for experimental use only.

In view of the toxicity of isoniazid and the uncertainty about the control of isoniazid-resistant strains of tubercle bacilli, this committee still recommends the use of streptomycin two or three days a week and PAS several times a day as the chemotherapy of choice in the treatment of most patients with tuberculosis.

[1] Developments in antimicrobial therapy of tuberculosis. A statement prepared by the Committee on Therapy, Am. Rev. Tuberc., 1952, *66*, 251.

David T. Carr
C. A. Castle
J. Maxwell Chamberlain
Nicholas D. D'Esopo
John B. O'Connor
Karl H. Pfuetze
Carl W. Tempel
William B. Tucker

Robert H. Ebert, *Chairman*

NOTES

NEW OFFICERS AT TRUDEAU SANATORIUM

Dr. Francis B. Trudeau, son of the founder of Trudeau Sanatorium at Saranac Lake, New York, has retired as president of the Sanatorium. He will continue as trustee.

Dr. J. Burns Amberson, Vice President of the Sanatorium, former president of the American Trudeau Society and the New York Tuberculosis and Health Association, will succeed Dr. Trudeau. Dr. Amberson brings to his new post a distinguished record of medical service. He is the former physician-in-chief of the Loomis Sanatorium at Liberty, New York, and is at present visiting physician in charge of the Bellevue Hospital chest service, and professor of medicine at the College of Physicians and Surgeons, Columbia University. Since 1935 he has been a consulting physician for the New York State Tuberculosis Hospitals, and since 1937 a consultant in pulmonary diseases to the State Department of Labor.

Other changes in the Trudeau administration were announced as follows: Albert H. Gordon, of New York City, becomes Chairman of the Executive Committee; George H. La Pan, of Saranac Lake, Treasurer; and William V. Griffin, of New York City, Vice President.

Trudeau Sanatorium, founded by Dr. Edward Livingston Trudeau in 1884 to accommodate patients with little means, was the pioneer tuberculosis sanatorium in the United States. Since its founding, it has treated more than 12,000 patients at less-than-cost care. The Sanatorium is supported by endowment and voluntary contributions.

FIFTIETH ANNIVERSARY OF THE HENRY PHIPPS INSTITUTE

During the week February 2–7, 1953, the Henry Phipps Institute of the University of Pennsylvania will celebrate its Fiftieth Anniversary. The Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis was founded in 1903 by the industrialist Mr. Henry Phipps, of Pittsburgh, whose interest in tuberculosis was stimulated by Dr. Lawrence F. Flick, of Philadelphia, a pioneer in the campaign against tuberculosis in this country and one of the founders of the National Tuberculosis Association. The Institute opened its doors for patients on February 2, 1903. It became a part of the University of Pennsylvania in 1909. On February 2, 1953, open house will be held at the Institute, in the building at Seventh and Lombard Streets, Philadelphia, in which the Institute has been located for the past forty years. On Friday, February 6, formal exercises will be held at the University of Pennsylvania, with an afternoon medical session and an evening banquet, tendered by the University of Pennsylvania for friends of the Institute and distinguished guests.

The Chairman of the Fiftieth Anniversary Program, who has arranged the celebration, is Dr. Frank A. Craig, Associate Director of the Henry Phipps Institute and Professor Emeritus of Clinical Medicine, a member of the Institute's original staff.

Principal speakers during the afternoon program on February 6 will be Dr. J. Burns Amberson, Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York City, who will speak on "The Treatment of Tuberculosis", and Mrs. Elizabeth K. Porter, Professor of Nursing, Western Reserve University, Cleveland, Ohio, who will speak on "Nursing in Tuberculosis." In the evening Dr. Thomas Parran, Dean of the Graduate School of Public Health, University of Pittsburgh, will speak on "The Prevention of Tuberculosis." Dr. Craig, Associate Director of the Institute, and Miss Fannie Eshleman, Director of Public Health Nursing, will take part in the afternoon ex-

ercises and discuss clinical and public health practice in tuberculosis. Dr. Norman Topping, Vice President in Charge of Medical Affairs of the University, will preside at the afternoon session. Dr. Esmond R. Long, Director of the Institute, will preside at the evening session. Mr. William H. DuBarry, Acting President of the University of Pennsylvania, and Mr. Robert T. McCracken, Chairman of the Board of Trustees, will address the guests of the evening on special phases of the Institute's work.

COURSES IN BRONCHO-ESOPHAGOLOGY AND PERORAL ENDOSCOPY

Two courses in Broncho-Esophagology and Peroral Endoscopy will be given at Temple University, February 23 to March 6, 1953, and in May, 1953. The fee is $250.00.

Further information and application blanks are available through Dr. Chevalier L. Jackson, 1901 Walnut Street, Philadelphia 3, Pennsylvania.

COURSES IN CLINICAL PHYSIOLOGY AND PULMONARY FUNCTION TESTS

A course in clinical physiology and pulmonary function tests will be given at the Graduate School of Medicine, University of Pennsylvania, March 16–21, 1953, under the direction of Dr. J. H. Comroe, Jr.

Special individual or small group conferences will be held as desired every evening and Saturday afternoon. These will be arranged personally during the course by the attending physicians and faculty. They are intended for those attending physicians who desire additional information—theoretical and practical—regarding any aspect of pulmonary function tests or pulmonary physiology.

Information concerning registration, tuition fees, et cetera may be obtained from the Dean, Graduate School of Medicine, University of Pennsylvania, Philadelphia 4, Pennsylvania.

PUBLIC HEALTH LABORATORY REFRESHER TRAINING COURSES

The following courses are being offered in 1953 at the Communicable Disease Center, Chamblee, Georgia:

Laboratory Diagnosis of Tuberculosis

March 16 to 27, and March 30 to April 3

November 9 to 13, and November 16 to 27

The one-week course is designed for laboratory directors, senior laboratory staff members, physicians, and others of comparable professional standing.

Laboratory Methods in the Study of Pulmonary Mycoses

November 30 to December 18

First consideration is given to personnel from laboratories of official health agencies and other nonprofit organizations.

Application forms can be obtained from the Laboratory Training Services, Communicable Disease Center, P. O. Box 185, Chamblee, Georgia, or from state health officers.

Books

THE PATHOGENESIS OF TUBERCULOSIS. Second Edition. By Arnold R. Rich. Pp. 1,018, with illustrations, Charles C Thomas, Springfield, Illinois, 1951, Price, $15.00.

There is little doubt that *The Pathogenesis of Tuberculosis* by Rich is a landmark not only in the literature of tuberculosis but also in the entire field of infectious diseases. There are few dissertations in the reviewer's acquaintance which exhibit the breadth of view, the integrative and dynamic qualities, and the critical and inclusive knowledge which characterize this monograph. At the same time, so fluid is the style and so lucid is the organization and presentation of the vast array of material considered that one reads this book with ease and absorbing interest. Only after the study of its approximately 900 pages of text and the 1,500 significant and representative original papers from all over the world during the last seventy years and more can one appreciate the vast storehouse of scientific studies which is evaluated and marshalled for the concepts developed by the author.

Considering the scope of this undertaking, which includes the nature and properties of tubercle bacilli and their products, the origin, progress, arrest, epidemiology, and prevention of tuberculosis, it is virtually impossible to integrate all these varied fields except on the basis of certain broad points of view. These concepts are naturally a reflection of the impact of the intellectual atmosphere in which the author lives and, particularly, of his own distinguished contributions to the understanding of the disease.

In 1944 the present writer reviewed the first edition of this work (Science, *100*, 407). It is now our task to evaluate the November, 1951, edition. In the first place, so much time elapses between the manuscript and the final appearance of a publication of this magnitude, and so rapid and varied has been the progress of recent studies bearing on this vast subject, that already some of the material is slightly behind. But this is unavoidable; no book is up to date at its appearance. The essential tenets of Dr. Rich on the pathogenesis of tuberculosis have been outlined in the 1944 review mentioned above. It was there stated that most of his conclusions will probably be widely accepted. In the second edition little fundamental change in concept is recorded. Some of the newer work has not been included, most likely because it appeared too late; other studies are omitted, perhaps because the author did not deem them sufficiently valid.

Here we shall consider only some of the ideas bearing on the essentials of the pathogenesis of the disease. Rich rightly draws a sharp distinction between virulence and resistance; the former being a property of the infectious agent, while the latter is a response of the invaded host. However, it is impossible to evaluate either alone as neither finds expression without the other. This is particularly cogent in his consideration of the nature of native resistance. While he repeatedly emphasizes that in a chronic infection like tuberculosis the native capacity to acquire resistance is of great importance in the course of the disease, he nevertheless fails to accept the view that the resistance of the rabbit to human-type tubercle bacilli is largely acquired during the course of the infection. Yet, it has been unequivocally demonstrated both by culture and histologic methods that the bacillus at first multiplies in the body of the rabbit before its destruction. This concept of resistance is seen with particular clarity in the response to human-type tubercle bacilli of highly inbred rabbit races which are genetically resistant and susceptible to bovine bacilli. For, while a natively susceptible animal will permit extensive and prolonged multiplication of the human bacillus in its lungs even for five months

after a quantitative inhalation, the resistant rabbit will destroy it almost completely after four weeks. Furthermore, even the attenuated BCG persists in the body of the natively susceptible race in much greater numbers and for a longer period than in the natively resistant family.

To Rich, the virulence of the bovine bacillus for the rabbit is entirely different in character from that of the human bacillus. It has been demonstrated, however, both quantitatively and qualitatively and by both histologic and cultural methods, that the rabbit destroys the bovine bacillus in the liver, spleen, and bone marrow after a preliminary multiplication just as it does the human-type, albeit more slowly. Yet the same rabbit dies from an unsuccessful struggle against the multiplication of this microorganism in its lungs and kidneys. It is noteworthy that the human bacillus is also destroyed with greater difficulty in the lungs and kidney of the rabbit. Incidentally, Rich himself, as well as others, has confirmed some of these observations by histologic procedure.

The pattern of resistance of the rabbit to both the human and the bovine bacillus is, therefore, fundamentally alike. It differs in each case as variations on a theme, only quantitatively with each type. True, the resistance to these two types of microorganisms are not identical. There are undoubtedly specific factors involved in each instance, such as the ultimate unknown qualities of each type which determine their differences in virulence. Nevertheless, the pattern of the resistance of the rabbit as a species to both types and of its individual organs to each are fundamentally controlled by their native capacities to acquire resistance. These usually come to expression in the very early days of the infection with the human type and later with the bovine type. Even in the first two weeks after an intravenous injection, it has been demonstrated that human and bovine bacilli accumulate more slowly in the liver than they do in the lung when these two organs are simultaneously flooded with either. This indicates that the lung permits the greater accumulation of both microorganisms than the liver at a time when specific immune factors have not yet been fully elaborated; hence, it must be concluded that the innate determinants of resistance are similar in both types of infection.

The present discussion is not merely of academic interest, for the resistance of man to tuberculosis is not an all or none entity; it is always a question of more or less, just like the rabbit's resistance to human-type tuberculosis. Therefore, the nature of the rabbit's resistance to tuberculosis is of essential importance in the understanding of human resistance to the disease.

That native resistance is essentially a capacity to acquire resistance and that this concept is of significance in the control of human tuberculosis has recently been demonstrated. If natively resistant and susceptible rabbits are simultaneously vaccinated with the same suspension of BCG, the protection afforded the susceptible animals against the inhalation of the human bacillus is negligible after a single vaccination, while the acquired immunity of the natively resistant stock is increased fivefold.

This brings us to a consideration of the role played by constitutional factors and that of the glands of internal secretion in native resistance to tuberculosis. In the Rich monograph, there is an enlightening chapter on the influence of age and sex on resistance to the disease. The author points out that the development of the mechanism for resistance is controlled by the age of the individual; he also presents evidence for the deleterious effects of pregnancy and menstruation on the disease. Apparently there was no opportunity to consider the studies which demonstrated the retarding effect of estrogen, on the one hand, and the enhancing influences of the corpus luteum function, on the other, in the dissemination of the disease in highly inbred animals of closely homogeneous native resistance to the infection.

Subsequently, studies on the role of other nonspecific hormonal factors in resistance

to infection have accumulated. These appeared after the publication of the monograph. Attention, nevertheless, is here called to these observations as they throw new light on the nature of genetic resistance to tuberculosis. It has been shown unequivocally that, not only do hormones affect the dissemination of the disease, but also that the adrenocortical steroids affect many of the known essential determinants which play a role in resistance to tuberculosis. Particularly important in this regard is the effect of excessive amounts of cortisone, namely, its enhancing effect on the multiplication of the bacilli within the macrophages. It is thus clearly seen that much of the resistance to tuberculosis and to other diseases as well is under the influence of entirely nonspecific hormonal factors which affect, not only the fate of the microorganism immediately after a first invasion of the tissues, but also the capacity of the host to acquire resistance during the course of the disease. It has been established with tuberculosis in rabbits as well as with typhoid infections in mice (Gowen) that acquired resistance is controlled by, and superimposed on, native resistance.

As to the mechanism of acquired resistance, most investigators will agree with Dr. Rich's revealing studies which largely demolish the old belief that immunity is solely a function of allergy. The evidence at hand indicates that allergy is not essential to the mechanism of acquired resistance. But it would be difficult to maintain that it may not aid in the resistance to the disease.

The reviewer is forced to restate his original unanswered objection to Rich's conclusion, that under no circumstances does allergy exercise any but a deleterious influence on the disease as it affects the growth or the dissemination of the microorganism from the portal of entry.

There is no doubt that agglutinating antibodies may be instrumental in delaying the transport of bacilli from the site of reinfection. This was pointed out and illustrated by the reviewer many years ago. However, nonspecific substances such as agar particles and trypan blue are more effectively fixed at the site of reinfection with tubercle bacilli in the guinea pig than in the rabbit. Antibodies cannot account for this difference. It is noteworthy that guinea pigs, despite their lower antibody-forming capacity, localize tubercle bacilli at these same sites more effectively than do rabbits. But the greater allergic sensitivity of the reinfected guinea pig accounts for the greater release of thrombokinase from the injured cells, which is sufficient to induce the clotting process in the former but not in the latter. It is during the active clotting of the exudate, as demonstrated by Opie, that foreign particles and tubercle bacilli are enmeshed in the fibrin threads and removed from the lymph, leaving the site of reinfection. The failure of tubercle bacilli to be fixed at an already formed area of inflammation in a nonallergic animal is no evidence against their entrapment during the clotting process which occurs rapidly at the site of reinfection and in its draining lymphatics in a highly sensitized animal.

It is clear, however, that allergy certainly is not a dominant factor either in native or acquired resistance. This is primarily a function of the mononuclear phagocytes although the body fluids also play a role. That entirely nonspecific factors are important in the intracellular growth of tubercle bacilli in the absence or presence of any specific antibodies has been demonstrated with cortisone. It is not surprising, therefore, that the initial multiplication of tubercle bacilli in the macrophages of a natively resistant rabbit is more restricted than in the macrophages of a natively susceptible animal. It is conceivable that the endocrine balance in the former inhibits the intracellular multiplication, whereas in the latter it favors it. Therefore, it is to be expected that in acquired resistance the same nonspecific factors also play a role.

In fact, it has been demonstrated that cortisone can abolish acquired immunity. It

was shown that mononuclear phagocytes derived from a tuberculous animal are physiologically more active than those from a normal animal. This was indicated by their greater rate of division in response to stimuli, their increased phagocytosis of tubercle bacilli suspended in normal serum, and their greater capacity for ingestion of entirely nonspecific particulates such as carbon, colloidion particles, and *Staphylococci*. It is noteworthy that increased adrenal function also increases this activity, and tuberculosis is associated with adrenal hypertrophy. Furthermore, immunization of rabbits with pneumococci has the same effect. Again, it has been shown by Lewis and Loomis that the antibody-producing mechanism is enhanced by a tuberculous infection toward entirely unrelated antigens such as sheep cells. It is interesting in this regard that excess cortisone paralyzes the digestive capacity of macrophages for red blood cells. Rich admits that the phagocytic activity of the macrophages of an animal with acquired immunity may at times be enhanced, but he assigns little significance to this or other enhanced physiologic activities of the mononuclear cells resulting from a tuberculous infection.

In his reasoning on the mechanism of acquired resistance in tuberculosis, Rich leans heavily on a possible analogy between it and that prevalent in the type-specific immunity of pneumococcus infections. While this approach has a definite heuristic value, as it prods us to find the specific antibodies involved in acquired resistance to the disease, there is no reason to adhere with such unyielding rigor to solely immunologic concepts today, when it is being increasingly revealed that constitutional factors are of such importance in the pathogenesis of infectious diseases. To underestimate the importance of such nonspecific phenomena as the demonstrated more rapid mobilization of mononuclear phagocytes at the site of reinfection is not quite in harmony with Rich's view: "there is no other known cellular or humoral mechanism that destroys tubercle bacilli apart from mononuclear phagocytes" (page 603).

It has been observed that mononuclear phagocytes derived from an immunized individual possess a greater inhibitory effect of the intracellular growth of bacilli than phagocytes derived from a normal animal even when the former are transferred to a normal host. There is no justification for dismissing these data on the mere opinion that cultural methods are not suitable for quantitative estimation of bacillary growth. This is particularly not tenable as the same conclusion is arrived at even by histologic methods, in which Rich places his trust. It is pertinent to state here that Suter has recently confirmed these studies by brilliant tissue culture procedures.

While native resistance, which in its early phase depends solely on nonspecific mechanisms, determines the level of acquired resistance resulting from a given immunizing process, it must be emphasized nevertheless that specific antibodies also probably operate in this acquired resistance. However, up to this time no such substances have been demonstrated. That these may resemble mechanisms responsible for allergic sensitivity which, as demonstrated by Chase, reside within the living cells of a sensitized animal and which, when transferred to a normal animal, confer sensitivity on the recipient is entirely possible. Such agents may specifically orient the increased physiologic activities of the phagocytes of an immunized animal to destroy or inhibit the growth of the ingested tubercle bacilli.

Concerning the role of acellular body fluids of immune animals in acquired resistance to the disease, Rich attributes the observed bacteriostasis of such fluids which penetrate colloidion-coated silk bags to an assumed increased inflammation which surrounds these in the immune and sensitized animal. But this was not the observation. On the contrary, the degree of inflammation about these structures in the normal animal was much greater and the bacillary growth in these situations was more pronounced. Indeed, if that were

the situation, it would constitute some evidence for the role of allergy in the suppression of the growth of the bacilli in the sensitized animal.

It is impossible and perhaps not quite in place to review all the tenets of this outstanding volume. It must be stated in all fairness, however, that Dr. Rich does not always consider with the same devotion data that are not entirely in harmony with his views as those that lead to his own convictions. Nevertheless, in view of the limitations of the size of the volume and the magnitude of the task, he has performed mightily even in this regard, and we await a new edition which will bring this fast-moving field more nearly to the then-existing state of knowledge.

MAX B. LURIE
Philadelphia, Pennsylvania

COLOR ATLAS OF MORPHOLOGIC HEMATOLOGY. By Geneva A. Daland. Edited by Thomas Hale Ham. Pp. 74, Harvard University Press, Cambridge, 1951, Price, $5.00.

This atlas has been published by the Harvard University Press and serves as an adjunct to their *Syllabus of Laboratory Examinations in Clinical Diagnosis*. Written by Geneva Daland and edited by Thomas Hale Ham, the book contains many practical aids in the examination of the formed elements of the blood.

The color reproductions and the text bring no sharper focus on the subject than has been achieved in available texts. Nonetheless, it is anticipated that this concise and well-organized presentation will enjoy increasing approbation in medical technology. It is a welcome companion piece to the syllabus already enjoying wide use. Laborious qualifications of description arising from the nature of morphology in hematology are at a minimum, yet the reader is not permitted to forget the reasons for their existence elsewhere. One perceives throughout a directness and simplicity of expression evolving from practical experience and critical evaluation of current methodology in hematology.

However, few books are without fault and there is some oversight in the reproduction and labeling of some representative blood smears. Would it not be more accurate to compare two blood smears which had been subjected to the same staining techniques? For example, red cells, stained vitally with brilliant cresyl blue then counterstained with Wright's stain are not best compared with red cells from another person treated only with Wright's stain (*viz.* Plates I, III, VII). Further on in the book the staining procedure is indicated on many of the color plates; however, some have not been so described. It seems important to label all plates as is customary in dealing with fixed and stained tissue sections.

In reference to sickle-cell anemia, the work of Pauling, Itano, and associates on the characteristics of hemoglobin in the sickling cell has been cited. Confusion arises from the present author's inference that mere examination of the Wright's stained blood smear corroborates the observations of this group, which point out a distinctive type of hemoglobin in these abnormal red cells.

With these few minor exceptions, the book promises to become a popular addition to the large library dealing with laboratory methods in clinical medicine.

CARL BERNTSEN, JR.
New York, New York

ADVANCES IN MEDICINE AND SURGERY FROM THE GRADUATE SCHOOL OF MEDICINE OF THE UNIVERSITY OF PENNSYLVANIA. Pp. 441, W. B. Saunders Company, Philadelphia, 1952, Price, $8.00.

This book consists of a series of symposia on subjects in which there have been notable advances and interest within recent years. The subjects covered are: adrenal cortical hormones, role of potassium, hypertension, preoperative evaluation and preparation of patients, thrombo-embolism, pulmonary infections, cancer problem, viral diseases, and functional disorders.

In dealing with each subject, the authors have devoted much space to the pertinent biochemistry, pathology, and physiology. It is written for the serious reader who desires a background in the pathogenesis of the subject as well as its clinical aspects.

The adrenal cortical hormones have been handled logically and comprehensively, not an easy task in view of the great amount of work that has been done on this subject in recent years. This can also be said of the section on potassium, which is presented in a readable fashion. The section on hypertension deals with the new depressor drugs, diets, and surgery in a conservative manner. The references provided are well chosen.

The authors, the Faculty of the Graduate School of Medicine of the University of Pennsylvania, with their experience in postgraduate teaching, are eminently qualified for this type of presentation.

James R. McMillan
New York, New York

Lung Abscess. By R. C. Brock. Pp. 190, Charles C Thomas, Springfield, Illinois, 1952, Price, $7.75.

This book is a monograph based on the study of clinical, anatomic, and pathologic features of patients with lung abscess who have been seen and treated by the author in his twenty years of experience as a thoracic surgeon.

Worthy of attention are the chapters on bronchopulmonary segmental anatomy and the pathology of lung abscess.

The clinical data must be read with reserve, partly because they are based on observations and experience of the pre-antimicrobial era and partly because of insufficient data. The chapter on Friedländer lung abscess is notably deficient in this respect.

Praiseworthy are the printing and well-reproduced diagrams and roentgenograms.

Alphonse E. Timpanelli
New York, New York

BOOKS RECEIVED

Pharmacology in Clinical Practice. By Harry Beckman. Pp. 839, with illustrations, W. B. Saunders Company, Philadelphia and London, 1952, Price, $12.50.

Toxoplasmosis. By Jacob Karl Frenkel and Saul Friedlander. Pp. 105, with illustrations, Federal Security Agency, Public Health Service, Microbiological Institutes of the National Institutes of Health, Washington, D. C., 1952, Price, 50 cents.

Anuario de Epidemiologia y Estadistica Vital—Ano 1948. Pp. 657, Servicio de Impresiones de la Division de Epidemiologia y Estadistica Vital del Ministerio de Sanidad y Asistencia Social, Caracas, 1952.

Tuberkulose-Jahrbuch 1950/1951. Pp. 244, with illustrations, Deutsches Zentralkomitee zur Bekämpfung der Tuberkulose, Springer-Verlag, Berlin-Gottingen-Heidelberg, 1952.

Diseases of the Chest. By T. Royle Dauber and Lloyd E. Hawes. Pp. 440, with illustrations, Williams & Wilkins Company, Baltimore, 1952, Price, $10.00.

THIS IS YOUR WORLD. By Harry A. Wilmer. Pp. 165, Charles C Thomas, Springfield, Illinois, 1952, Price, $5.50.

A 40 YEAR CAMPAIGN AGAINST TUBERCULOSIS. By Louis I. Dublin. Pp. 115, Metropolitan Life Insurance Company, New York, 1952.

REPORT OF LOCAL PUBLIC HEALTH RESOURCES—1950. Pp. 75, Federal Security Agency, Public Health Service, Washington, D. C., 1952.

CONTROLLED MATERIALS PLAN AND HEALTH FACILITIES—July 1, 1951–June 30, 1952, Division of Civilian Health Requirements, Public Health Service, Federal Security Agency, Washington, D. C., 1952.

ARTHRITIS—AND THE MIRACLE DRUGS. By Alton L. Blakeslee. Pp. 32, Public Affairs Committee, Public Health Service, Federal Security Agency, Washington, D. C., 1952.

DER TUBERKULOSEABLAUF IM KÖRPER. GRUNDLAGEN DE PHTHISIOGENETISCHEN ANALYSE. By Reiner W. Müller. Pp. 170, with illustrations, Georg Thieme Verlag, Stuttgart, 1952.

THE WHITE PLAGUE. By René and Jean Dubos. Pp. 277, Little, Brown and Company, Boston, 1952, Price, $4.00.

TREPHINE TECHNIQUE OF BONE MARROW INFUSIONS AND TISSUE BIOPSIES. Sixth Edition. By Henry Turkel. Pp. 78, 650 West Boston Blvd., Detroit, Michigan, 1952.

YOU AND TUBERCULOSIS. By James E. Perkins and Floyd M. Feldmann; in collaboration with Ruth Carson. Pp. 176, Alfred A. Knopf, Inc., New York, 1952, Price, $2.50.

THE AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

Edited by LAWRENCE B. HOBSON

VOLUME 67 FEBRUARY, 1953 ABST. NO. 2

CLINICAL STUDIES, TUBERCULOSIS

Prognostic Value of Spinal Fluid Findings.—The findings in the cerebrospinal fluid from 68 patients with tuberculous meningitis before and after streptomycin treatment were used to determine their prognostic value. Comparison of the laboratory data with the death rate shows that the higher the chloride concentration before streptomycin treatment, the better the prognosis. Thus, of 26 patients with an initial chloride concentration of 540 to 660 mg. per 100 cc., 88 per cent died; of 12 patients with an initial concentration between 700 and 740 mg. per 100 cc., the mortality was only 33 per cent. Patients with a high protein concentration of 100 to 2,000 mg. per 100 cc. before treatment had a mortality rate of 75 per cent; the number of recoveries and deaths was approximately the same among patients with an initial protein concentration between 10 and 100 mg. per 100 cc. No prognostic value could be demonstrated for the number of cells or the globulin concentration. During treatment with intraspinal streptomycin, changes in the chlorides correlated with clinical improvement; the quicker the fall in the chloride concentration, the better the prognosis. Among the successful cases, 70 per cent had normal chloride values from one to three months after streptomycin therapy was started; only 5 per cent of the fatal cases showed such normal values. Less prognostic importance can be attributed to the albumin concentration since it becomes normal in patients who overcome the infection only after three to five months of treatment with antibiotics. Persistence of albumin and cells in the spinal fluid of patients who appear otherwise cured might be partly attributed to the local irritation caused by the intraspinal injections. Relapses are characterized by a sudden increase in the number of cells and in the protein concentration coincident with the appearance of clinical symptoms and with no preceding changes in the spinal fluid.—*Il liquor nelle meningiti tubercolari trattate con streptomicina, G. Mescolini, Lotta contro tubere. November–December, 1951, 11–12: 559.*—(*A. Mochi*)

Sequelae of Primary Tuberculosis.—Primary childhood tuberculosis frequently leads to pulmonary sequelae, among which is a sclerocystic atrophy with juxta-hilar rarefaction. Among 230 sanatorium admissions there were 49 of such cases. The commonest site is the anterior segment of the upper lobe, usually on the right. At the onset the lesion appears as a homogeneous segmental condensation accompanying a bronchial lesion and nearly always associated with ventilatory difficulties. The lesion gradually retracts and then undergoes a process of sclerocystic atrophy. Pleural adhesions appear to play an essential role in the genesis of these bronchiectases. The diagnosis is roentgenographic, so it is important to take routine lateral films and postero-anterior tomograms which include sections near the anterior wall. The prognosis depends upon the bacteriology since, on the one hand, persistent tubercle bacilli may be demonstrated in the lesion by culture or guinea pig inoculation; or, on the other hand, the area may become secondarily infected with banal pyogenic organisms. It is to be hoped that early and complete treatment of the initial lesion will reduce the frequency of these cases which may be disturbing and even dangerous. Once established, segmental or lobar resection seems the only logical treatment although it has rarely been performed.—*Les images claires juxta-hilaires du poumon,*

sequelles de la tuberculose initiale chez l'enfant, P. Lowys & M. Nahum, Poumon, May, 1952, 8: 383.—(F. S. Lansdown)

Tuberculosis in Identical Twins.—Primary tuberculous infection occurred simultaneously in identical female twins at the age of seven. The peculiar and identical localization of the primary focus and the protracted course without clinical signs of activity caused considerable diagnostic difficulties (Author's summary).—*Primartuberkulose bei eineiigen Zwillingen, F. Fierz., Schweiz. Ztschr. Tuberk., 1952, No. 1: 42.—(E. Dunner)*

Tuberculous Reinfection.—The authors conclude from roentgenographic and endoscopic observations that the perforation and fistula formation from bronchial lymph nodes into the bronchial system play a larger role in the pathogenesis of bronchopulmonary reinfection in the adult than has hitherto been supposed. Thus, it would be likened to the pathogenic process so well known in infant tuberculosis (Author's summary).—*Zur Frage der Entstehung der Lungenphthise des Erwachsenen aus perforierenden Hiluslymphknoten, F. Suter & H. Iselin, Schweiz. Ztschr. Tuberk., 1951, No. 4: 341.—(E. Dunner)*

Tuberculous Chancre.—Primary tuberculous infections on the female genitalia are not common but such an infection of the penis is extremely rare. A 29-year-old man working in the ragshop of a textile mill noticed a small infiltration on the glans penis. It grew slowly and later ulcerated. When he was admitted to the hospital, the ulcer was approximately 2 cm. in diameter. It had a hard painless base, moist granulations, and a superficial yellowish membrane. The inguinal lymphatic glands were swollen. Laboratory tests for syphilis were completely negative. Since carcinoma was a possibility, the ulcer as well as the swollen inguinal lymphatic gland were biopsied. Histologic examination revealed tuberculosis. Streptomycin, 1 gm. daily, healed the lesions in fifty days. The source of infection remained undiscovered. The patient had no other tuberculous process and his wife was healthy. The patient denied any extramarital sexual contact.—*Primary tuberculous chancre (Czech), M. Dvorak, Lék. listy, August 1, 1952, 7: 385.—(J. Ilavsky)*

Ureterocolostomy for Tuberculous Cystitis.—Three patients with tuberculous cystitis had small, sclerotic bladders which caused intense pain, incontinence, and loss of sleep. After all other therapy had failed, each obtained substantial relief from ureterocolostomy of the Coffey I type.—*Ureterocolostomy as treatment for tuberculous sclerotic urinary bladder (Yugoslav), S. Petkovic, Tuberkuloza, January–April, 1952, 4: 27.—(J. Ilavsky)*

Ocular Scrofulosis.—A review of the literature and a statistical study of 42 cases of ocular scrofulosis, combined with generalized tuberculosis, showed that the ocular syndrome has no prognostic significance. The frequency of tuberculous reactivation was not increased by the presence of the ocular lesions (Author's summary).—*Über die Kerato-Conjunctivitis skrofulosa beim Kinde und ihre Bedeutung für die tuberkulöse Allgemeinerkrankung, H. U. Widmer, Schweiz. Ztschr. Tuberk., 1952, No. 1: 47.—(E. Dunner)*

Lower Lobe Cavities.—From 1945 to 1950, 2,865 tuberculous patients were treated in the Sanatorium Topolsica. Cavities were present in the lower pulmonary lobes in 117 (4 per cent) of them. Bed rest alone gave good results in 3 of 8 cases, antibiotics in 5 of 9 cases, pneumothorax in 6 of 16, phreniclasia in 18 of 37, pneumoperitoneum in one of 4, pneumonolysis in 3 of 6, and various combinations of therapy in 17 of 37 cases. Lower lobe cavities of short duration responded to treatment with bed rest and temporary collapse measures. Older and larger cavities required resection.—*Therapy of lower lobe cavities in Topolsica, 1945–1950 (Yugoslav), I. Cestnik, Tuberkuloza, January–April, 1952, 4: 83.—(J. Ilavsky)*

Henoch's Purpura in Tuberculosis.—A tuberculous man, admitted to the hospital for pneumonolysis, had a history of purpura

hemorrhagica following hemorrhoidectomy. An extrapleural pneumonolysis was performed without difficulty or immediate complications. Thirteen days later extensive purpura appeared on the legs and forearms but the platelet count remained well above that in purpura hemorrhagica. During the next few days the lesions disappeared, only to reappear a week later. The entire body, except the face, was purpuric and the patient steadily failed until he died on the twenty-third day of his exacerbation. Because Henoch's anaphylactoid purpura is so regularly fatal in patients with active tuberculosis, extreme caution should be used in operating upon tuberculous patients with a history of purpura.—*Anaphylactoid purpura following surgical treatment of tuberculosis* (*Slovak*), *A. Haninec, Lék. listy, August 1, 1952, 7: 375.*—(*J. Ilavsky*)

Streptokinase and Streptodornase in Tuberculosis.—Streptokinase and streptodornase act superficially to produce a selective chemical debridement, and the best results have been obtained when an infected area could be completely exteriorized. If this is not possible, the means for drainage should be as adequate as possible. Necrotic tissue must be removed because it prevents satisfactory contact of the enzymes with the constituents of the wound. Sloughing tissue may contain trypsin which inactivates streptokinase. Toxic effects have as yet not been seen when the enzymes have been applied to external wounds. Four patients with tuberculous empyema, 5 with tuberculous lymphadenitis, and 10 with some manifestation of tuberculosis of the bones, joints, or tendons were treated. In 16 of the 19 patients, the tuberculous infection has been controlled and all wounds and sinuses are healed. In the remaining 3 patients, local improvement was obtained in the presence of systemic progression of the disease. The rapidity of healing that is afforded by surgical drainage of tuberculous abscesses, when it is combined with the use of enzymes, offers a more satisfactory way of treating these lesions than older conservative methods. Streptokinase and streptodornase must be used purely as adjuncts, however, to other therapeutic measures. If spontaneous closure of wounds does not occur rapidly, secondary closure may then be carried out.—*Clinical experience with streptokinase and streptodornase in tuberculosis, J. M. Müller, P. H. Long, & E. S. Stafford, J. A. M. A., April 26, 1952, 148: 1485.*—(*H. Abeles*)

Bed Rest and Cavity Closure.—Cavities closed satisfactorily in the lungs of tuberculous patients while they were receiving a modified rest cure and certain antibiotics as conservative measures before or instead of collapse therapy or resection. This treatment alone was not continued if the cavities did not close promptly. At the sanatorium at Sijsele, the patients rested in bed twenty-four hours a day but were not completely inactive. Since the patient's morale was considered as important as his rest, he was allowed to read, do handicraft, or study as an avocation so long as he remained horizontal. A total dose of 30 gm. of streptomycin was first used with 12 gm. of *p*-aminosalicylic acid (PAS) daily. Later, the streptomycin was reduced to 15 or 20 gm. administered in 1 gm. doses every two or three days to avoid leukopenia, which occurred in 3 cases. The patient's condition was evaluated with blood tests and radiography, especially tomography. The patient was mobilized gradually in a planned fashion while his condition was regularly followed. A first evaluation was usually made three weeks after the rest treatment was begun, and a second evaluation was made six weeks later. If the results were favorable, the regimen was continued for another two months; if unfavorable, collapse therapy or resection was considered. In successful cases, treatment lasted nine or ten months, including gradual mobilization over five or six months. In 1949, of 360 cavities being treated, 156 closed in the lungs of 100 patients. In 1950, the results were also satisfactory among the 157 patients treated. The results varied with the number and size of the cavities. Of 56 cavities in a group of 50 patients with bilateral cavitation, 29 (50 per cent) closed. Conservative rest therapy should be given a wider trial to avoid unnecessary chest surgery if the essential precautions are rigidly applied.—*Le traitement*

des cavernes par le repos complet et les antibiotiques, A. Gyselen & P. Mannes, Acta tuberc. belg., June, 1952, 43: 157.—(A. T. Laird)

Pneumoperitoneum.—During the past five years, 17 authors have reported on the therapeutic results of 3,349 cases of pneumoperitoneum. No improvement was mentioned in 23 per cent of the cases, improvement occurred in 42.4 per cent, and improvement with closure of cavity in 34.6 per cent. The author, in adding his 26 cases to the series, mentions the following advantages of pneumoperitoneum: good tolerance even in serious bilateral cases, reversibility, and little or no damage to respiratory function. In combination with a phreniclasia, the pulmonary function tests reveal a diminution in complementary air, whereas pneumoperitoneum alone diminishes exclusively the residual air. Chemotherapy is recommended as an adjunct to pneumoperitoneum.—*Das Pneumoperitoneum in der Behandlung der Lungentuberkulöse, St. J. Leitner, Schweiz. Ztschr. Tuberk., 1951, No. 4: 175.—(E. Dunner)*

Intrapleural Pneumonolysis.—The major complications following intrapleural pneumonolysis at the Laennec Hospital in Paris for 1947 through 1951 comprise four groups: (*1*) pleural effusions with serofibrinous pleurisy or empyema but without bronchopleural fistulas; (*2*) bronchopleural fistulas; (*3*) rigidity or ballooning of a cavity; and (*4*) severe postoperative accidents such as shock or asphyxia. Of 690 intrapleural pneumonolyses, 240 were performed from 1946 to 1947; 350 from 1949 to 1950; and 100 during the first part of 1951. The incidence of complications during these three periods was 17.9 per cent, 4 per cent, and 1 per cent; the mortality following operation and its complications was 3.75, 0.85, and 0 per cent, respectively. Improved operative techniques cannot explain the improved results. The use of streptomycin preoperatively and at the onset of complications since 1948 has definitely played a part, as has an increasing awareness of the danger of difficult and prolonged pneumonolyses, of large, peripheral cavities, and of very active tuberculous processes. The major factor in decreasing complications has been the use of "delayed pneumothorax" rather than "early pneumothorax." At present the patient is put on strict bed rest and given streptomycin, 1 gm. every three days, with *p*-aminosalicylic acid, preferably as intravenous infusion, 15 gm. daily. Frequently, pneumoperitoneum is instituted after the most acute initial symptoms have subsided. After three weeks of this treatment, the case is re-evaluated with tomographic and cultural examinations. If there is persistent cavitation, pneumothorax is induced at this point and pneumonolysis can then be performed with a minimum of complications.—*La régression des complications secondaires aux section de brides pleurales, E. Bernard, J.-L. Herrenschmidt, & J. Weil, Rev. de la tuberc., 1952, 16: 297.—(V. Leites)*

Pneumonolysis in Children.—Collapse therapy was used to close cavities in a series of children although pneumothorax was often difficult. Pleural adhesions were common and required surgical treatment, usually thoracoplasty or pneumonolysis. Since the former caused irreversible changes in the respiratory and circulatory systems as well as deformity, pneumonolysis seemed preferable. Within a year, 9 pneumonolyses were performed on children ten to fourteen years old. As compared with adults, the children tolerated the operation well and had no respiratory or circulatory difficulties; technically, the operation was easier because of the lighter muscles, finer ribs, shorter duration of the disease, and more readily freed pleura; and the postoperative course was more benign. Large hematomas did not form; exudates disappeared in ten to twenty days; fever decreased; and the patients improved promptly. Cavities closed rapidly; and tubercle bacilli disappeared from the sputum soon after the operation. Reinsufflation of the extrapleural pneumothorax was easy and there was almost no exudate. A year after operation, no new tuberculous foci had appeared in the lungs. In spite of these good results, definite conclusions cannot be drawn from so small a series or from observations during only one year.—*Pneumonolysis in*

children (Yugoslav), M. Grujic & I. Cabak, Tuberkuloza, December, 1951, 3: 561.—(J. Ilavsky)

Extrapleural Pneumothorax.—Extrapleural pneumothorax is important in the treatment of cavernous tuberculosis of children and adolescents. In 41 operations upon 37 patients, there were 2 postoperative deaths from hemorrhage, 2 nonspecific empyemas, and one bronchopleural fistula. In all of the patients the cavity closed, and in only 2 with endobronchial tuberculosis the sputum remained positive (Author's summary).—*Die Extra Pleurale Pneumolyse im Kindesalter, V. Vojtek & Zdenek Sery, Schweiz. Ztschr. Tuberk., 1952, No. 3: 141.—(E. Dunner)*

Surgery for Tuberculous Empyema.—Thoracoplasty sometimes should precede pleural decortication because the former decreases the space in the thorax, preventing overexpansion of the decorticated lung and the resulting emphysema which may reactivate latent tuberculous foci. Thoracoplasty favors reexpansion of that part of the lung which has been collapsed by an empyematous pneumothorax and may cure the empyema before decortication. Closure of cavities before the decortication reduces the operative risk and an antecedent thoracoplasty facilitates resection at the time of decortication. Of 15 decorticationsperformed during 1951 at the Tuberculosis Hospital in Golnik, 12 resulted in healing and 2 in improvement; one patient died in heart failure. Empyema had been present one to seven years before operation.—*Therapy of tuberculous pleural empyema: Decortication of the lung in the treatment of chronic tuberculous empyema (Yugoslav), S. Krstic, Tuberkuloza, January-April, 1952, 4: 3.—(J. Ilavsky)*

Fatality Following Plombage.—An extrapleural pneumothorax was created in a patient and 3 polyethylene sacs were placed in it. Five months later the patient developed cough, retrosternal pain, and expectoration of extremely fetid material, associated with regurgitation of ingested fluids. At a second operation the lateral wall of the pocket was found to consist of almost stony hard fibrous tissue. A fistula joined the pocket, which contained foul pus, with the trachea and esophagus. The largest of the polyethylene sacs impinged on and nearly occluded the fistulous tract to the esophagus. Great difficulty was encountered in closing the esophageal defect. The patient died of mediastinitis the day following operation.—*Complication mortelle d'un plombage extra fascial à l'aide de sachets de polythène. Fistule œsophago-trachéoextra fasciale, J.-J. Pariot & J. Demirleau, Poumon, May, 1952, 8: 423.—(F. S. Lansdown)*

Pneumonectomy for Destroyed Lung.—Among 22 patients subjected to pneumonectomy for "destroyed lung" with cavitary or caseous lesions which involved all lobes entirely, there were 6 fatalities, 2 of them surgical and 4 tuberculous. Of the 16 survivors, 11 may be considered cured, 4 having been followed more than two years postoperatively and the remainder for more than one year. All of these have a roentgenographically normal remaining lung, are in an excellent general state, and none has discharged tubercle bacilli since the operation. The results were analyzed in relation to pre-existing conditions: (*1*) The proportion of cure among patients with bronchial stenosis was actually higher than among those without it. (*2*) Among patients with strictly unilateral disease, there were more deaths and fewer cures than among those with contralateral lesions. When a contralateral lesion existed, it cleared readily following operation. (*3*) The appearance of activity of the disease proved to be the most important factor in prognosis and should be considered an absolute contraindication to the operation in that all 3 patients whose disease was unstable died of tuberculous complications.—*Pneumonectomies pour poumon detruit tuberculeux, J. Mathey, F. Tobe, & G. Oustrières, Poumon, May, 1952, 8: 433.—(F. S. Lansdown)*

CLINICAL STUDIES, NONTUBERCULOUS DISEASE

Influenza A[1] Infection.—Between January and March, 1951, 106 patients with the clinical diagnosis of influenza were admitted to

the U. S. Naval Hospital in Philadelphia. The diagnosis of an influenzal virus infection was accepted when the following criteria were met: (*1*) presence of serologic evidence of recent infection by the influenzal virus; (*2*) demonstration of a clinical course compatible with such infection; (*3*) absence of bacterial pathogens as etiologic agents. Detailed data on 76 patients with influenza A^1 were obtained. Of these, 24 (31.6 per cent) showed pulmonary infiltrations. The average age of the entire group was 26.5 years; the average age of those with infiltration was 22.3 years. The onset was sudden in 59 (77.6 per cent), gradual in 17 (22.4 per cent). The symptoms were "upper respiratory" in 21 (27.6 per cent), "lower respiratory" in 36 (47.4 per cent), "constitutional" in 19 (25 per cent). The symptoms did not differentiate the cases with pulmonary infiltrations from those without infiltrations; physical signs were of help. The cold agglutinin titers were not helpful in establishing the diagnosis. Complement-fixation determinations for influenza A and A^1 were more reliable. Of 24 patients with roentgenographic infiltrations, 11 (45.8 per cent) showed bronchitic lesions; 7 (29.2 per cent), peribronchitic lesions; 5 (20.8 per cent), alveolar infiltrations; and one (4.2 per cent), lobar consolidation. Antibiotics had little therapeutic effect in patients with infiltrations as well as in those without infiltrations.—*Virus influenza A^1 infection with pulmonary manifestations, J. M. Scher & E. Jaruszewski, A. M. A. Arch. Int. Med., August, 1952, 90: 201.*—(*G. C. Leiner*)

Syphilis of the Lung.—A pneumonectomy was performed in a patient with a presumptive diagnosis of carcinoma. Examination of the specimen revealed a gumma. Tertiary syphilis of the lung is uncommon but not rare. The patients are in relatively good health. Cough is noted in 88, expectoration in 71, and hemoptysis in 37 per cent of the patients. There are few abnormal physical signs but other luetic stigmata should be sought. Pathologically, there are two types, fibrous and gummatous. The fibrotic type may be the end stage of healed gummata and may present a nonspecific appearance. Gummata are usually multiple. They usually develop at least ten years after the primary infection. Aortitis is a frequent accompaniment. Radiologically, there are 4 types: (*1*) inert fibrosis, (*2*) gummatous-like tumor, (*3*) pneumonic or atelectatic in infants or children and (*4*) glandular. The gummata shrink with antisyphilitic therapy. The blood serological reaction is helpful in diagnosis but is not conclusive. It is to be remembered that many cases of tuberculosis show positive serological tests for syphilis.—*Tertiary syphilis of the lung and its diagnosis, A. D. Morgan, W. E. Lloyd, & C. Price-Thomas, Thorax, June, 1952, 7: 125.*—(*A. G. Cohen*)

Clostridial Pneumonia.—A patient underwent a partial gastrectomy for duodenal ulcer. Three days later, there was evidence of a fulminating pneumonia. Despite penicillin and sulfamerazine, an empyema developed during the third week; culture of the fluid yielded *Cl. welchii*. Treatment with anti-gas-gangrene serum and penicillin intrapleurally was then instituted. Eventually, the patient improved and finally recovered. During the later part of the illness, culture of a nasal swab yielded a heavy growth of *Cl. welchii*. A nasal spray of penicillin was used to combat this infection. It was believed that this was the original focus.—*Primary clostridial pneumonia, A. E. O'Donnell, Lancet, August 23, 1952, 2: 367.*—(*A. G. Cohen*)

Transient Lung Infiltration.—Transient lung infiltrations, closely followed by transient blood eosinophilia, can follow the parenteral administration of vegetable oils. The clinical manifestations correspond to the syndrome described by Löffler with few clinical manifestations and a benign course. The infiltrations always suggest hematogenous dissemination, with frequent hilar enlargement and, rarely, pleural involvement. The blood eosinophilia is not only relative but absolute, and occurs simultaneously with bone marrow eosinophilia. The etiologic significance of the parenteral ad-

ministration of oil has been demonstrated. Pathogenetically, the lung infiltrations may be caused by oil microembolism. The blood eosinophilia is considered an expression of the eosinophilic resorptive inflammatory reaction elicited by the activity of the tissue lipase in the vicinity of the oil depots (Authors' summary).—*Flüchtige Lungeninfiltrate mit Blutcosinophilie nach therapeutischen Ölinjektionen, W. Löffler, A. F. Esselier, G. deMeyer, & L. Morandi, Schweiz. med. Wchnschr., August 2, 1952, No. 31: 777.—(E. Dunner)*

Hemoptysis.—A history of hemoptysis was obtained in 200 of 670 patients who were bronchoscoped. A malignant tumor of the trachea, bronchus, or lung was present in 29.5 per cent of the 200 cases. Bronchiectasis was present in 26.5 per cent. In 17 cases the cause of the hemoptysis could not be determined. In cases in which a thorough clinical investigation fails to disclose any cause for the hemoptysis, there is an excellent chance that a serious pulmonary lesion will not develop subsequently. The severity of the bleeding gives no indication of the nature of the underlying disease.—*Clinical significance of hemoptysis, H. J. Moersch, J. A. M. A., April 26, 1952, 148: 1461.—(H. Abeles)*

Talc Pneumoconiosis.—A 65-year-old man had been employed in the handling and packaging of elastic cord coated with talc powder for a period of twenty-four years. No exhaust or ventilating fans were present in the work room. He complained of a cough of many years' duration. His chest film showed emphysema and diffuse pulmonary fibrosis with a large pleural plaque in the right upper lobe area.—*Talc pneumoconiosis, P. S. Friedman, M. A. Bell, & L. Solis-Cohen, J. A. M. A., April 19, 1952, 148: 1418.—(H. Abeles)*

Gasoline Pneumonia.—A patient accidentally inhaled liquid gasoline and collapsed. Later there was evidence of bronchopneumonia which rapidly resolved. A few cases have previously been reported. The effects have been classified as immediate, general, and delayed. The immediate effects are due to bronchial irritation. The general effects are due to the absorption of gasoline into the blood stream, with exhilaration, drowsiness, cyanosis, and unconsciousness. The delayed effects are wandering pneumonia, hemorrhagic pneumonia, pneumonitis, and pleural effusion. These have been known to last as long as two months.—*Petrol pneumonia, A. W. Husband & M. Gelfand, Lancet, August 16, 1952, 2: 351.—(A. G. Cohen)*

Chronic Cor Pulmonale and Pancreatic Fibrocystic Disease.—Pulmonary complications are common in fibrocystic disease of the pancreas. Extensive alteration and destruction of the pulmonary parenchyma may occur, causing chronic cor pulmonale which is present in 70 per cent of infants and children who die from fibrocystic disease of the pancreas. The clinical histories and autopsy reports indicate that 2 children had fibrocystic disease, bronchopneumonia, bronchiectasis, chronic cor pulmonale, and right heart failure. The diagnosis of cor pulmonale in children is usually difficult. Chemotherapy and cardiac therapy are of little benefit.—*Chronic cor pulmonale as a complication of fibrocystic disease of the pancreas, C. E. Tomlin, R. B. Logue, & J. W. Hurst, Am. Heart J., July, 1952, 44: 42.—(G. C. Leiner)*

Idiopathic Pneumothorax and Permeable Pleura.—In 4 patients, idiopathic pneumothorax was diagnosed on the basis of thoracoscopy. It is believed that in these cases the air entered the pleura through the thin pleural layer over pulmonary blebs without rupture of the blebs. These blebs are usually caused by tuberculosis. Pneumonolysis should be done in order to abolish the valvular mechanism which causes the high pressure in the blebs. Thickening of the thin pleura can be achieved by local irritation with streptomycin or talcum.—*Luftaustritt aus der permeablen Lunge beim Spontanpneumothorax, H. O. Suess, Wien. klin. Wchnschr., August 1, 1952, 64: 554.—(G. C. Leiner)*

Spontaneous Chylothorax.—In each of 5 cases of chylothorax not due to any direct trauma or to other obvious cause, there was evidence of some previous condition which could have caused fixation of the thoracic duct to the vertebrae. In 4 of the 5 there was a history of some subsequent sudden movement that could have caused hyperextension of the vertebral column. It is believed that these 2 factors are insufficient in themselves to cause rupture of the duct and that a third one is necessary. The third factor, purely hypothetical, is increased fragility of the thoracic duct. This could be due to the same cause that produced fixation of the duct or to some other factor. Two of the 5 patients were successfully treated by ligation of the thoracic duct just above the diaphragm; 3 were successfully treated by closed drainage of the chylothorax. In the first patient whose duct was ligated, a contralateral chylopneumothorax developed three years later and responded to closed drainage. The second patient, whose chylothorax was controlled by closed drainage after 2 unsuccessful attempts to find and ligate the thoracic duct, died as a result of fulminating hepatitis after five months and was found at autopsy also to have widespread lymphosarcoma. In the treatment of chylothorax, simple aspiration should be tried first for a few days. If no real improvement results, closed drainage should be established and tried for a week. Failure of this procedure requires operation on the thoracic duct. Resection of a portion of the duct and ligation of the ends should be done, rather than simple ligation alone. It is hoped that in the future efforts will be made to resect the injured part of the duct, so that more information about the causation of chylothorax may be obtained (Author's summary).—*Spontaneous chylothorax: Observations on its pathogenesis and management based on study of five cases, R. W. Meade, A. M. A. Arch. Int. Med., July, 1952, 90: 30.*—(*G. C. Leiner*)

Mediastinal Goiter.—Within twenty-eight years 6 women were seen in whom a mediastinal goiter caused serious symptoms. Transsternal strumectomies were done in these cases. This method seemed to be less dangerous than the attempt to remove the mediastinal goiter from the neck. The operation was successful in all cases.—*Mediastinale Kröpfe und die transsternale Strumektomie, Wien. klin. Wchnschr., August 1, 1952, 64: 545.*—(*G. C. Leiner*)

Nonspecific Fibrous Pericarditis.—A patient, whose disease seems to meet all criteria of recurrent nonspecific pericarditis, had a history of antecedent respiratory infection before each of five episodes of classical pericarditis, the first two unrecognized. Aureomycin was apparently of value in treating the last recurrence of acute pericarditis. There never was evidence of other cardiac disease, congestive failure, rheumatic fever, or tuberculosis. Evidence has appeared that the patient now has fibrous or adhesive pericardium which may later become constrictive. This suggests that the pericaridum may become scarred during repeated episodes of acute nonspecific pericarditis, which should be considered a cause of constrictive pericarditis rather than an entirely benign disease.—*Acute nonspecific pericarditis complicated by the development of a fibrous pericardium, J. J. Freilich, Ann. Int. Med., 1952, 37: 388.*—(*T. H. Nochren*)

Carbon Monoxide Uptake.—In man the rate of carbon monoxide uptake in relation to pulmonary performance follows the simple exponential equation for respiratory exchange of inert gases. The rate of uptake varies directly with atmospheric concentration because the physiologic "solubility" of carbon monoxide in blood increases with decreasing atmospheric concentration of the gas. The rate of uptake is independent of the pulmonary circulation rate. At rest, it is primarily dependent upon lung ventilation. During hard exercise, the diffusion area of the lungs does not increase in proportion to the rise in ventilation rate. Consequently, the rate of carbon monoxide uptake is approximately equally dependent upon ventilation rate and diffusion capacity (Author's summary).—*Carbon monoxide uptake in relation to pulmonary per-*

formance, T. F. Hatch, A. M. A. Arch. Indust. Hyg. & Occup. Med., January, 1952, 6: 1.—(T. H. Noehren)

Surgical Treatment of Pulmonary Hypertension.—Pulmonary hypertension with or without increased pulmonary blood flow is present in many patients with congenital heart disease. Recent evidence indicates that the lumens of the small muscular pulmonary arteries often decrease in diameter with these deformities as the result of increased pulmonary artery pressure and blood flow, and that this is progressive. Pulmonary stenosis was successfully created in 2 patients in order to impose a point of high resistance proximal to the smaller pulmonary arteries. A large atypical patent ductus was closed in each of 4 infants, 3 of whom were in cardiac failure; a large inter-auricular septal defect was also repaired. The pressures in the aorta and pulmonary arteries were measured directly in most of the patients and lung biopsies were taken. An attempt was made to correlate the pulmonary artery pressure and the changes in the small muscular pulmonary arteries with the nature of the malformation and the age of the patient. Only medial hypertrophy of the smaller pulmonary arteries was present in the infants, but in the older patients intimal fibrosis became more marked with age. The creation of pulmonary stenosis to relieve pulmonary hypertension should be considered in patients in whom the cardiovascular deformity is such that the heart functions physiologically as a single ventricle or when the pulmonary resistance increases as a result of medial thickening with or without moderate intimal fibrosis. It should not be produced when extreme intimal fibrosis is present until it can be determined whether this process is reversible.—*The surgical significance of pulmonary hypertension, W. H. Muller, Jr. & J. F. Dammann, Jr., Ann. Surg., September, 1952, 136: 495.—(M. J. Small)*

Primary Pulmonary Arteriolosclerosis.—Primary pulmonary arteriolosclerosis, also known under the name of Ayerza's disease, occurs rarely. To 28 cases in the literature, 3 are added. In 2 of these the diagnosis was made at autopsy; in the third, by lung biopsy. The etiology is not known. It may be that pulmonary arteriolosclerosis is caused by hypoxia and that the usual cause of this hypoxia is pulmonary hypertension. "Primary pulmonary hypertension" may be the correct name for this disease. The first symptoms are usually referable to the respiratory tract; they are followed by the symptoms of right heart failure. The most frequent symptoms and signs are dyspnea, cyanosis, cardiac enlargement, peripheral edema, hepatomegaly, precordial pain, orthopnea, hemoptysis, somnolence, clubbing of the digits, and compensatory polycythemia. The earliest roentgenographic finding is an accentuated pulmonary conus-artery segment; later right ventricular hypertrophy develops. No specific therapy is known. The pathologic diagnosis is one of exclusion; all the factors causing secondary arteriolosclerosis must be absent. The pathologic findings are hypertrophy and dilatation of the right ventricle with evidence of congestion due to right heart failure with fibrous intimal thickening of the pulmonary arterioles. —*Primary pulmonary arteriolosclerosis, L. F. Parmley, Jr. & F. S. Jones, A. M. A. Arch. Int. Med., August, 1952, 90: 157.—(G. C. Leiner)*

Carcinoma *in Situ* and Lung Cancer.—Among 60 lungs which were resected for epidermoid and undifferentiated carcinoma, 13 showed unquestionable carcinoma *in situ* and 8 had anaplastic hyperactivity of the intact bronchial epithelium. Thus, in 35 per cent of the cases, one or the other of these lesions was found adjacent to invasive carcinoma of the lung. In all of these, the tumor was central in origin, arising in one of the lobar bronchi or in one of their major segmental divisions. In all but 7 of the 60 cases, advanced squamous metaplasia of the bronchial epithelium was found. The microscopic sections reviewed were, for the most part, random ones and no attempt was made to demonstrate epithelial changes at the periphery of the tumors. In 2 cases, carcinoma *in situ* was demonstrated in the lung opposite the main tumor. There is

serious question whether lobectomy should ever be used for bronchogenic carcinoma if carcinoma *in situ* has been demonstrated, even though the lymph nodes are normal at operation. Thus, in one case, carcinoma was clinically limited to the right upper lobe but, in the resected lung, carcinoma *in situ* extended down into the intermediate bronchus; the regional lymph nodes were free of metastases on microscopic examination. If considerable basal cell hyperactivity and anaplasia are found in a specimen, carcinoma should be suspected and sought for, especially by cytologic examinations of the sputum. Among the 13 cases of bronchogenic carcinoma with epidermoid carcinoma *in situ*, a positive cytologic diagnosis was made in 10, 2 were highly suspicious, and only one was negative. —*The importance of epidermoid carcinoma in situ in the histogenesis of carcinoma of the lung, H. Black & L. V. Ackerman, Ann. Surg., July, 1952, 136: 44.*—(*M. J. Small*)

Intrathoracic Tracheal Tumors.—Intrathoracic tracheal tumors should be suspected when patients, particularly men between the ages of forty and seventy, present themselves with a history of cough, expectoration, dyspnea, and wheezing. In 3 of 4 cases reported by the authors, the diagnosis of asthma was entertained; chest roentgenograms were negative in all. The more common pathologic types of tracheal tumor are squamous cell carcinoma and cylindroma. The latter offer better opportunities for surgical resection since they are slow growing. A cylindroma had been present in one case for nine years and in another for six years before resection. In neither case was there evidence of metastasis at the time of operation. These tumors tend to infiltrate and eventually to metastasize even after fairly radical excision. Tracheal tumors tend to develop in the lower third of the trachea where they are most readily accessible, but in each of the 4 cases reported the tracheal tumor was resected. Three were cylindromas and one was a squamous cell carcinoma. One patient died of bronchopneumonia six days after operation and one died two years after operation with local recurrence and extensive pulmonary metastasis. One patient is alive and well eleven months after operation, and one is alive and well one year after operation.—*Intrathoracic tracheal tumors: Development of surgical technics for their removal, O. T. Clagett, H. J. Moersch, & J. H. Grindlay, Ann. Surg., September, 1952, 136: 520.*—(*M. J. Small*)

Fatal Bronchial Polyp.—A 43-year-old man had shortness of breath, cough, and expectoration. The chest roentgenogram showed the heart and mediastinum shifted to the left, the left diaphragm higher than the right, and a massive density over the left lung field. At autopsy, massive atelectasis of the left lung was found to be due to a bronchial polyp the size of the small finger.—*Bericht über einen Fall von tödlich verlaufener Bronchusstenose durch gutartigen Bronchuspolypen, C. Ziemer, Ztschr. f. Tuberk., 1952, No. 5-6: 308.*—(*E. Dunner*)

Kymography and Foreign Bodies.—Intrathoracic foreign bodies, especially those in or near the heart, are not frequent in peacetime, but the number of known cases might be greater if exhaustive studies were made whenever they were suspected. Intracardiac foreign bodies cannot be excluded by lack of symptoms or clinical findings, since penetration of the myocardium can occur without serious hemorrhage or alarming tamponade. Hemothorax or empyema may completely obscure this more serious pathology. Routine roentgenograms in more than one plane must, therefore, be supplemented by others with overpenetration and, when possible, by roentgenoscopy. If a foreign body is found, meticulous study is required before cardiac surgery. Such study can be enhanced by using kymography which shows distinctive heart and vessel waves even in the presence of juxtacardiac pathology, such as empyema, hemothorax, or pyoneumothorax. An opaque foreign body within the lung but adjacent to the cardiac silhouette should move continuously with the vascular waves transmitted to it. Due to the elastic-

ity of lung tissue, however, the foreign body should definitely be displaced away from the heart or great vessels. If the foreign body were in the pericardium or myocardium, this displacement should not occur and the motion should be even more characteristic of its specific vascular location. No characteristic kymographic picture should be anticipated for a foreign body within a cardiac chamber but the picture should differ, depending on whether the foreign body were free or within a thrombus.—*Roentgen kymographic localization of intrathoracic foreign bodies, A. H. Joistad, Am. J. Roentgenol., August, 1952, 68: 216.*—(*T. H. Nochren*)

Homalograph.—A new apparatus for stratigrams, called the homalograph, employs an immobile focus and a rotating patient and film instead of a mobile system of focus and film with an immobile object. The patient is fixed on a rotating chair, the film rotating in the same direction and at the same speed.—*Eine neue Methode zur Herstellung von Röntgenschichtaufnahmen, T. Wedekind & E. Wetzels, Schweiz. Ztschr. Tuberk, 1952, No. 3: 129.*—(*E. Dunner*)

Bronchography in Iodine Sensitivity.—A patient with definite iodine sensitivity and suspected bronchiectasis was hospitalized for bronchographic study. The patient received 20 mg. of corticotropin twice a day for four days and then 10 mg. daily for five days. On the third and fourth days of desensitization, bronchographic studies were carried out using iodochloral. There was only a slight reaction lasting several hours which in no way compared with previous reactions which had lasted as long as four days.—*Bronchography in iodine sensitivity, P. A. Theodos, J. A. M. A., April 19, 1952, 148: 1419.*—(*H. Abeles*)

ANTIMICROBIAL THERAPY

Clinical Results with Isoniazid.—Of 45 patients with stationary or progressive active pulmonary tuberculosis daily given 4 to 8 mg. of isoniazid per kg. of body weight, 23 have been treated for eight to ten weeks, 11 for six to seven weeks, and 11 for four to six weeks. A group of 50 patients treated with streptomycin and *p*-aminosalicylic acid (PAS) served as controls. The dosage of isoniazid was, in general, well tolerated. Transitory side effects due to the drug included atonic obstipation, urticarial exanthema, a slight decrease in blood pressure, and an increased desire for sleep. Subjectively, there were also an increase in appetite, a feeling of well-being and a decrease in the toxic symptoms of the disease. Urinalysis showed no change except an increase in urobilinogen in a few patients. There was no significant alteration of the red and white blood cell counts. The hemoglobin concentration dropped approximately 10 per cent. Of 27 patients with increased sedimentation rate, 4 showed a return to normal; 8, a decreased rate; and 15, an unchanged value. One of the most striking effects of isoniazid therapy was a decrease in cough and expectoration accompanied by a parallel decrease in the number of tubercle bacilli. This effect, however, was transitory. The fourth to sixth week of therapy was apparently the most favorable phase. After this period the tubercle bacilli were no longer morphologically abnormal. After eight weeks of therapy, tubercle bacilli could again be cultured from the sputum or gastric contents of patients whose cultures earlier had revealed no growth. Roentgenographic improvement was less marked and less frequent in the isoniazid-treated group. Among 34 patients treated for seven to ten weeks with isoniazid, 7 showed marked improvement as compared with 30 of 50 patients who received streptomycin and PAS. Both groups showed an equal percentage of moderately improved, 28 per cent. No improvement was noted in 17 of 34 isoniazid-treated patients compared with only 6 of 50 patients treated with streptomycin and PAS. Isoniazid was thought to be less effective in the closing of cavities.—*Vergleichende Frühergebnisse der Rimifon Behandlung bei Lungentuberkulose, O. Düggeli & F. Trendelenburg, Schweiz. Ztschr. Tuberk., 1952, No. 4: 267.*—(*E. Dunner*)

Clinical Results with Isoniazid.—A series of 60 patients with pulmonary tuberculosis were treated with isoniazid, 4 to 6 mg. of the drug per kg. of body weight usually being given daily for four to fourteen weeks. In 3 patients the dose was increased to 10 to 15 mg. per kg. without additional therapeutic effect. In 30 patients severe toxic symptoms subsided. The appetite improved in many cases and the patients gained weight. Decrease of fever, cough, and expectoration was frequently observed. Within fourteen weeks, twenty-one of 40 patients converted their sputum to negative as judged by smears of concentrates, 13 also by cultures. Roentgenographic observations showed a decrease in cavity size in 14 of 48 cases with cavitary disease; resorption and induration of exudative foci also occurred. Three cases of laryngeal tuberculosis improved considerably. In tuberculous pleurisy in the presence of a therapeutic pneumothorax, refills could be continued. Slight temporary decrease of the erythrocyte count was seen in 12 patients; mild eosinophilia in 8. A patient who received ephedrine at the same time as isoniazid developed dyspnea, cyanosis, and cerebral excitation.—*Isonikotinsäurehydrazid in der Behandlung der Lungentuberkulose (vorläufiger Bericht), A. Balogh, Wien. klin. Wchnschr., August 22, 1952, 64: 598.*—(*G. C. Leiner*)

Isoniazid for Tuberculous Meningitis.—Four children with tuberculous meningitis were treated with isoniazid. One child received isoniazid alone; she became well within a week and had a normal cerebrospinal fluid in eight weeks. Three other cases received streptomycin initially, followed by isoniazid alone or with streptomycin; the results were equivocal. —*Isonicotinic acid hydrazide in the treatment of tuberculous meningitis in children, W. P. Sweetnam & E. F. Murphy, Lancet, July 26, 1952, 2: 160.*—(*A. G. Cohen*)

Tuberculous Meningitis.—After four years, 5 deaths have occurred and 9 patients have recovered among 14 adult patients with tuberculous meningitis treated with streptomycin. Of the 9 who recovered, 6 are completely free of all symptoms. All of the 5 fatalities and 3 patients who recovered had generalized miliary tuberculosis preceding their meningitis. The early use of intrathecal streptomycin therapy was thought to be the most important factor in the successful cases. Results were good in those who received intrathecal therapy within three weeks of the onset of meningitis; whereas, in the 5 patients who died, intrathecal therapy was not initiated until three months after the onset of meningitis. Infusions of large quantities of liquids containing *p*-aminosalicylic acid seemed to reduce the possibility of spinal block. The administration of high doses of vitamins A and D is strongly recommended. The concentrations of the sugar and protein in the cerebrospinal fluids are prognostically significant; persistence of a low sugar and a high protein concentration is unfavorable.—*Beitrag zur modernen Behandlung der tuberkulösen Meningitis beim Erwachsenen, E. R. Mordasini, Schweiz. Ztschr. Tuberk., 1951, No. 4: 253.*—(*E. Dunner*)

Treatment of Vestibular Damage.—Clinical and pathologic observations suggest that vestibular damage due to streptomycin proceeds in stages and progresses from the peripheral to the central nervous system. Response to therapy confirms that there exist (*1*) an early histaminergic phase (after 1.0 to 30 gm. of streptomycin) in which antihistaminic agents are effective and permit continuation of the antibiotic in the great majority of cases, (*2*) a secondary neurotoxic and vascular phase (after 30 to 90 gm.) in which ergotamine tartrate leads to rapid cure in three-fourths of the cases, and (*3*) a late central nervous system involvement leading to serious and persistent sequelae. The etiology of the last phase seems to be the moderate but frequently repeated courses of treatment. Genoscopolamine gives complete relief in 30 per cent of cases and partial but sufficient amelioration in 50 per cent of the remainder. Dihydrostreptomycin sulfate or hydrochloride in general causes trouble which appears later but is

as serious and, moreover, is accompanied by irreversible auditory lesions. For this reason it seems better at present to use streptomycin as often as possible in spite of vestibular difficulties, these being reversible and largely amenable to treatment (Author's summary).—*Traitement étagé des troubles vestibulaires dus a la streptomycin, J. Martin-Lalande, Poumon, May, 1952, 8: 403.—(F. S. Lansdown)*

Initial PAS Resistance.—At the Tuberculosis Institute in Golnik, Yugoslavia, tubercle bacilli were tested for their sensitivity to *p*-aminosalicylic acid (PAS) by (*1*) indirect assays on glycerin agar with egg yolk, (*2*) modified Price microcultures, and (*3*) direct assays on Löwenstein-Jensen medium. The last method was preferred. As has been found elsewhere, PAS resistance appeared later and more gradually than streptomycin resistance and the two were not necessarily coincidental. In one case a PAS-resistant strain of tubercle bacilli was cultured from a patient who never had received PAS.—*Testing of the resistance of tubercle bacilli to PAS (Yugoslav), K. Krstic-Arco, Tuberkuloza, January-April, 1952, 4:* 73. —*(J. Ilavsky)*

Intermittent PAS.—Since 1949, the authors have followed a treatment schedule patterned after the combined, intermittent streptomycin-*p*-aminosalicylic acid (PAS) regimen recommended by the U. S. Veterans Administration, Army, and Navy Chemotherapy Conferences, with the following variation. Instead of 12 gm. of PAS daily, 10 gm. of PAS were prescribed on the first day, 12 gm. of PAS on the second day, and no PAS on the third day. It was correctly anticipated that the omission of PAS every third day would permit better toleration of the medication. After a ninety-day period of treatment of 150 patients, it appeared that (*1*) clinically, the results equalled those obtained when daily streptomycin had been prescribed; (*2*) bacteriologically, there was no noteworthy increase in the emergence of resistance to either streptomycin or PAS; (*3*) subjective side reactions were few, and there was no evidence of neurotoxic damage.—*Die intermittierende Kombinationstherapie der Lungentuberkulose mit Streptomycin und Paraaminosalicylsäure, E. Tanner, E. Wiesmann, & P. Baer, Schweiz. med. Wchnschr., March 8, 1952, No. 10: 250.—(E. Dunner)*

Intracavitary Calcium PAS.—Forty-two patients received 3,500 injections of calcium *p*-aminosalicylate (PAS) directly into the cavitary component of their tuberculous disease. The daily injections consisted of 2 cc. of a 7 per cent calcium PAS solution. If the size of the cavity remained unchanged after 60 injections, streptomycin was added parenterally or directly into the cavity. The patients included 26 men and 16 women between the ages of seventeen and fifty-seven. One patient had two cavities. The results observed in these 42 patients with 43 cavities indicate that 10 cavities were lost to view; 18 became markedly smaller; 5 remained unchanged. Complications due to the procedure were few. Spontaneous pneumothorax occurred in 3 patients; air embolus in one. It is concluded that the intracavernous injection of PAS can be considered only as a preparatory step for the conventional collapse measures.—*Erfahrungen mit intracavitarer Aminacyl-Injektions-behandlung tuberkuloser Lungenkavernen, Hirsch, Schweiz. Ztschr. Tuberk., 1951, No. 3: 159.—(E. Dunner)*

PAS for Intestinal Tuberculosis.—Three patients with clinical and roentgenologic evidence of intestinal tuberculosis were treated with *p*-aminosalicylic acid (PAS). The drug was generally given as the sodium salt, 12 to 16 gm. daily, for four to five months. Striking clinical and radiological improvement occurred in all 3 cases. In 2 cases, symptoms, signs, and roentgenographic abnormalities disappeared entirely, while in the third and most severe case minimal abnormalities persisted. Improvement was first noted a few weeks after the start of the PAS and continued as late as several weeks after the completion of the course. No toxic manifestations due to the drug were noted except abdominal cramps and diarrhea, which disappeared as soon as

the PAS was temporarily withheld. It was not necessary to discontinue the drug permanently. Since far advanced pulmonary disease was still present in all the cases after the completion of the course of PAS, a return of the signs and symptoms of intestinal tuberculosis is a definite possibility. It is concluded that PAS is a useful drug in the treatment of intestinal tuberculosis. Its use is indicated in streptomycin-resistant patients and in patients from whom it is advisable to withhold streptomycin in order to retain streptomycin sensitivity for the future management of the pulmonary disease (Author's summary).—*The use of para-aminosalicylic acid (PAS) in the treatment of intestinal tuberculosis, I. N. Wolfson, Ann. Int. Med., 1952, 36: 1475.*—(*T. H. Noehren*)

Amithiozone for Bone Tuberculosis.—Observations made on 219 patients with bone and joint tuberculosis indicate that in the 49 patients who received amithiozone there was a marked increase in the further dissemination of tuberculosis as compared with the group of patients who did not receive this additional therapy. The administration of amithiozone in low daily doses may increase the virulence of the tubercle bacilli.—*Tuberkulöse Streuung unter der Behandlung chirurgischer Tuberkulosen mit TB1/698 (Tebethion), K. Treppinger, Ztschr. f. Tuberk., 1952, No. 3-4: 177.*—(*E. Dunner*)

Antimicrobial Therapy in 1952.—Some accepted principles of antimicrobial therapy for tuberculosis can now be stated with considerable confidence. (*1*) Most patients with an active tuberculous infection should receive antimicrobial drugs at some stage of treatment; not all patients with active disease should be so treated, as some physicians advocate. (*2*) Such treatment should be prolonged, continuous, and maintained for a considerable time after all evidence of activity of the disease has disappeared. (*3*) Streptomycin and *p*-aminosalicylate (PAS) should be used concurrently, rather than in sequence, in order to defer the appearance of bacteria resistant to the drugs. (*4*) Streptomycin need not be administered every day, for similar results may be obtained when it is given every third day. (*5*) Surgical extirpation of some destructive tuberculous lesions may well be deferred until many months of medical therapy have resolved all reversible disease. (*6*) Principles established for pulmonary tuberculosis appear to apply to some types of extrapulmonary tuberculosis as well. (*7*) Principles established for streptomycin and PAS are likely to apply to other bacteriostatic drugs. The author's experience with isoniazid (isonicotinic acid hydrazide) in more than 100 patients indicates that it is not a curative drug, for it does not rapidly eradicate tuberculous infection but acts as a symptomatic remedy and as a bacterial suppressive agent in much the same manner qualitatively as do streptomycin and PAS.—*Antimicrobial therapy of tuberculosis in 1952, H. C. Hinshaw, Ann. Int. Med., 1952, 37: 362.*—(*T. H. Noehren*)

Drug Action on Intracellular Tubercle Bacilli.—Macrophages collected from the peritoneal cavity of the rabbit can be kept alive *in vitro* for ten to twenty-one days. These cells ingest *M. tuberculosis*, and the effects of drugs on the intracellular organisms can be observed. The growth of tubercle bacilli ingested by macrophages which contained particulate micrococcin was somewhat retarded; a "solution" of micrococcin made by means of Triton and incorporated in the nutrient medium was slightly more effective. Neither form of micrococcin completely prevented intracellular growth. Streptomycin hydrochloride at a concentration of 10 γ per ml. in the culture medium completely inhibited growth of a bovine strain (Branch) of tubercle bacilli but 25 γ per ml. were needed to inhibit the growth of a human strain (H37Rv). A concentration of 50 γ per ml. did not kill all intracellular bacilli in seven days. Terramycin, neomycin B, and viomycin were bacteriostatic for intracellular bacilli at concentrations of 12.5, 25, and 100 γ per ml., respectively. *p*-Aminosalicylic acid did not inhibit the bovine strain completely even at 100 γ of cul-

ture medium per ml. Nisin was without effect at 50 γ per ml. Penicillin at concentrations of from 31 to 1,000 γ per ml. appeared to stimulate rather than inhibit growth. Bacilli whose growth was inhibited remained unaltered in appearance for six days; thereafter they began to stain poorly and to become smaller, but digestion by the cells was not complete in eleven days. It was impossible to determine at what stage this viability was lost.—*The action of drugs on intracellular tubercle bacilli, G. B. Mackaness, J. Path. & Bact., July, 1952, 64: 429.—(H. J. Henderson)*

Characteristics of Resistant Tubercle Bacilli.—Comparative studies of growth characteristics of streptomycin-resistant strains, both highly resistant and slightly resistant, were made using a technique of microculture in a moist chamber. The cultures were grown both on ordinary media and on media containing various amounts of streptomycin. Morphologically, growth was similar with and without streptomycin. The strains did not consist of uniformly resistant cells but included some more sensitive organisms. The latter were affected morphologically by streptomycin concentrations exceeding their sensitivity just as other sensitive organisms are affected. At the time of inoculation of the culture medium, the sensitive and resistant cells did not differ morphologically. Streptomycin resistance was shown to be specific in an experiment in which penicillin and sulfathiazole had identical effects on the morphologic characteristics of the resistant and sensitive strains.—*Studies on streptomycin-resistant strains of the tubercle bacillus: II., E. Espersen, Acta path. et microbiol. Scandinav., 1951, 29: 211.—(H. G. Turner)*

Stilbamidine for Blastomycosis.—Systemic blastomycosis is an infrequent but serious disease which usually occurs in the third through the fifth decades of life among poor persons, particularly men. Farmers are more frequently affected than other groups. Any organ can be involved, but the sites of predilection are the skin and subcutaneous tissues, the lungs, the bones or joints and, less commonly, the central nervous system. Initial respiratory symptoms occur in half the cases. The mortality for patients with proved or presumptive blastomycosis has been 78 per cent. Treatment has been unsatisfactory. Iodides, desensitization with vaccine followed by iodides, arsphenamine followed by iodides, cauterization, excision, and radiation have been suggested. Penicillin alone or with streptomycin has been ineffective. Stilbamidine and propamidine were beneficial in 3 cases and gave encouraging results in a fourth, although therapy could not be completed. The total amount of stilbamidine required for a cure is not known, but probably 4.5 to 6 gm. administered in two or three courses are sufficient. The patients in this series received 6, 5.5, 4.5, and 2.2 gm. of stilbamidine, respectively, the last being inadequate. *Blastomyces dermatitidis* could still be isolated from this last patient after the total of 2.2 gm. Trigeminal neuropathy became evident in 3 of the cases and was annoying but not disabling. No other evidence of toxicity was observed. Propamidine has been used locally to advantage but should not be given parentally because of its toxicity.—*The treatment of systemic blastomycosis with stilbamidine, E. B. Schoenbach, J. M. Miller, & P. H. Long, Ann. Int. Med., 1952, 37: 31.—(T. H. Nochren)*

Aureomycin for Pleural Infections.—Nine patients with nontuberculous bacterial infections of the pleural space received aureomycin at some time during the course of treatment. The organisms involved included *D. pneumoniae, Streptococcus, H. influenzae,* and a paracolon organism. Two patients who had infections from a pneumococcus and a beta hemolytic *Streptococcus,* respectively, recovered completely when treated with aureomycin and aspiration only. In 5 other patients, the antibiotic was believed to have a beneficial effect. In the remaining 2 patients, it was impossible to evaluate the effect of aureomycin. The drug seems to be an excellent therapeutic agent for empyema if adequate drainage is first established. Without such

drainage, relapses, pleural fibrosis, and limitation of pulmonary function are likely to occur. Aspirations, with or without streptokinase and streptodornase, are as successful as thoracotomy if evacuation is complete. Aspirations can be less frequent with aureomycin therapy than with intrapleural instillations of penicillin. The concentration of aureomycin was measured in 11 specimens of pleural fluid from 6 patients. A therapeutically significant concentration was usually present twenty-four hours after the beginning of oral therapy. In general, the antibacterial action of the pleural fluid was 25 to 50 per cent that of the blood, although in several instances it equaled that of the blood. Four specimens of pericardial fluid from 2 patients gave similar results.—*Treatment of nontuberculous bacterial pleural space infections with aureomycin: Results of treatment in nine patients; concentration of aureomycin in pleural and pericardial fluid in seven patients, C. K. Wolfe, M. H. Lepper, E. R. Caldwell, H. W. Spies, & H. F. Dowling, Ann. Int. Med., 1952, 37: 164.—(T. H. Nochren)*

Penicillin - Resistant Staphylococci.—Increasing numbers of penicillin-resistant strains of *Staphylococci* are encountered in hospitals in many countries. Cross infection is believed to account for the spread of such resistant strains. The noses and throats of 1,000 school children, fourteen to fifteen years old, were routinely cultured for diphtheria organisms and the cultures were utilized to isolate the *Staphylococci* present in their throats. The number of resistant strains was then determined since the opportunity for cross infection with penicillin-treated, resistant strains was considered to be less than in a group of hospitalized patients. Pathogenic *Staphylococci* were present in all but 17 per cent of the patients. Of these, 94.6 per cent harbored organisms sensitive to penicillin. There were 3.9 per cent with highly resistant organisms (up to 5.7 units per ml.) and only 1.5 per cent with relatively resistant strains (between 0.17 and 5.71 units per ml.). Only a part of this group had been treated with penicillin but this does not account for the different incidence of resistant strains in these subjects and that in a series of hospitalized patients in which 18.8 per cent of the strains were highly resistant and 8.7 per cent relatively resistant. The results suggest a greater opportunity for cross infection in hospital patients.—*The incidence of penicillin-resistant pathogenic Staphylococci isolated from the respiratory tract of young healthy persons, T. M. Vogelsang, Acta path. et microbiol. Scandinav., 1951, 29: 363.—(H. G. Turner)*

Bacitracin for Staphylococcic Lung Abscess.—A 62-year-old white man, after undergoing a cholecystostomy, developed postoperative atelectasis and pneumonia. In spite of administration of penicillin, streptomycin, chloramphenicol, terramycin, and sulfadiazine, abscesses appeared in the left lower lobe. A sputum culture yielded hemolytic *Staphylococcus albus*, which was found sensitive to bacitracin but resistant to penicillin, dihydrostreptomycin, terramycin, and chloramphenicol. Complete cure resulted from bacitracin given intramuscularly, 10,000 units every four hours for seven days, 10,000 units every eight hours for fourteen days. Nephrotoxic effects due to bacitracin were observed; they disappeared after discontinuance of the drug.—*Acute staphylococcic lung abscess cured with aid of bacitracin, R. Charet & I. Siegel, A. M. A. Arch. Int. Med., August, 1952, 90: 250.—(G. C. Leiner)*

LABORATORY STUDIES

Cortisone and Pseudotuberculosis in Rats.—In the course of a study of the effects of corticotropin and cortisone on tuberculosis in various animals, an unusual disease was observed in certain albino rats. Extensive necrosis similar to tuberculous lesions developed only in rats injected with cortisone alone or with cortisone and, later, avian tubercle bacilli. In contrast to these results, the disease was not encountered in rats given large quantities of corticotropin. The causative agent of this unexpected infection was *Corynebacterium pseudotuberculosis murium*, the bacterium of pseudotuberculosis. Normal rats

are not highly susceptible to this microorganism, relatively large intracardiac inocula being required to produce the disease. Pseudotuberculosis occurred in 41 of 50 rats given cortisone; in 28 of 30 instances in which isolation was attempted, *Corynebacteria* were recovered. The infection was the apparent cause of death in 30 of the 41 rats in which it appeared. There were widespread necrotizing lesions in the lungs with multiple coalescent areas, and similar, although smaller, lesions of the pericardium, pleurae, liver, and kidneys. The gross appearance of the pulmonary disease was similar to that of a disseminated, far advanced tuberculous process. Histologically, however, the lesions were distinctive and readily differentiated from true tuberculosis. The experimental infection with avian tubercle bacilli was not markedly altered by the factors which led to the emergence of the pseudotuberculosis. The pathogenesis of the latter disease has not been established. Whether the animals which received cortisone were already harboring the microorganism before receiving cortisone or whether the cortisone rendered them uniquely susceptible to airborne infection remains unanswered. *Corynebacteria* could not be isolated from normal rats or from the air of the animal rooms. The bacteria were, however, isolated from pulmonary tissues of 6 of the 9 animals which received cortisone without developing pseudotuberculosis. Repeated tests for sterility revealed no *Corynebacteria* in the cortisone. It can only be said that the administration of cortisone transformed most of the rats into uniquely susceptible hosts for *C. pseudotuberculosis murium* and favored the development of lesions in the lungs and other viscera. —*The emergence of pseudotuberculosis in rats given cortisone, C. LeMaistre & R. Tompsett, J. Exper. Med., April 1, 1952, 95: 393.*—(*J. S. Woolley*)

Middlebrook-Dubos Test.—The Middlebrook-Dubos test for circulating hemagglutinins was studied in four groups of patients and animals. The first group of human sera was from 428 consecutive hospital patients, of whom only 15 per cent had clinical tuberculosis. Of these 428 patients, 223 (52 per cent) had a positive test for circulating hemagglutinins; of the 362 who were nontuberculous, 182 (50 per cent) had positive tests. The second group of sera was from patients who were being treated for active tuberculosis. In this group of 9 patients were 3 whose tuberculosis became worse. In one, titers gradually rose to high levels, in the second they varied considerably, and in the third they remained constant at medium levels. Titers of one patient whose disease remained stationary gradually rose from a moderate to a high level. Among the 5 whose disease improved, weekly titers rose, fell, remained constant at a low level, or were variable. None of the 9 patients ever had negative serologic tests. The other groups consisted of guinea pigs infected intraperitoneally and rabbits inoculated intra-ocularly with *M. tuberculosis* H37Rv. The test results failed to parallel the course of tuberculosis in either humans or animals.—*Some observations upon the Middlebrook-Dubos hemagglutination test in man and animals, P. Bunn, J. Gino, C. Adair, & L. Canarili, Ann. Int. Med., 1952, 37: 84.*—(*T. H. Noehren*)

Toxicity of Penicillin for Tubercle Bacilli.—Since penicillin has been added to sputum concentrates to reduce contamination, experiments were conducted to see whether such a procedure would affect the growth of tubercle bacilli. Sputums containing very few bacilli were employed and penicillin was added to the neutralized concentrates so as to give 100, 200, and 400 units per ml. of concentrate. The smallest amount of penicillin appreciably diminished the colony count as compared with that in tubes without the drug. With 400 units, only one-half the colonies appeared. It made little difference whether the exposure to penicillin was for less than a minute or for fifteen minutes. This suppressing effect of the penicillin would, of course, present no serious problem in specimens containing large numbers of tubercle bacilli but might result in false negatives when there are only a few

bacilli.—*Toxic effect of penicillin on the culture of tubercle bacilli, J. R. Fallin, R. A. Patnode, & A. K. Hudgins, Am. J. Clin. Path., July, 1952, 22: 703.*—(*J. S. Woolley*)

Germination and Growth of BCG.—By removing serially small sections from an agar plate and viewing them directly under the microscope, the growth rate and the percentage of germination were studied in several batches of BCG vaccine. Preliminary studies indicated that there is a definite pattern of both the percentage of germination and of the growth rate. This method might be used quantitatively as a measure of minimal standards for BCG vaccine.—*Germination and growth of BCG vaccine followed by the direct agarmicroscopy on Dubos media I, J. Orskov & H. C. Engbek, Acta path. et microbiol. Scandinav., 1952, 30: 395.*—(*H. G. Turner*)

Efficacy of Centrifugal Concentration of Sputum.—Various workers have noted that tubercle bacilli in sputum digested with sodium hydroxide are not completely sedimented at the ordinary centrifuge speeds. To test the efficacy of centrifugation, sputa containing varying numbers of tubercle bacilli were subjected to routine concentration procedure. An aliquot of 5 ml. was digested with sodium hydroxide, neutralized with hydrochloric acid, and centrifuged. Both the sediment and the top layer of the supernatant fluid were cultured. In one series, more than 400 sputa were centrifuged at 2,000 r.p.m.; cultures of the sediment revealed 97 per cent of the total positives; and those of the supernatant, 88 per cent. In a similar series, centrifuged at 3,000 r.p.m., the detection rates were 97 and 82 per cent, respectively. Sometimes more colonies grew from the top layer than from the sediment. In 2 or 3 per cent of the specimens, bacilli grew only from the supernatant. Cultures from 100 digested and homogenized specimens before centrifugation were negative in only 2 specimens for which cultures of the sediment were positive. Thus, most but not all of the tubercle bacilli in the sputa had specific gravities greater than that of the suspending fluid. Although the denser tubercle bacilli were thrown outward during centrifugation, only those bacilli close to the bottom reached the sediment. Prolonged centrifugation at high speeds would be required to carry bacilli from the upper layers of fluid completely to the sediment. A thorough examination should include culture or animal inoculation of the supernatant fluid.—*Efficacy of centrifugation as a method of concentrating tubercle bacilli, G. C. Klein, M. Maltz, M. M. Cummings, & C. H. Fish, Am. J. Clin. Path., June, 1952, 22: 581.*—(*J. S. Woolley*)

Serologic Studies on H. Pertussis.—Studies were carried out to help establish which characteristics of *H. pertussis* strains are most significant when selecting a strain for vaccine production. Definite serologic differences were demonstrated between freshly isolated strains of *H. pertussis*, the antigenic characteristics being constant among strains obtained during a brief sequence of infections. *H. pertussis*, *parapertussis*, and *bronchisepticus* were definitely related and had identical thermostable "O" antigens and hemorrhagic toxin; each possessed its own specific "K" antigen as well as overlapping "K" antigens. The specific "K" antigens indicate a method for typing strains of *H. pertussis*. In mice, immunity was stronger after infection than after vaccination but there was no demonstrable difference in the immunizing effect of serologically different strains. Although variants differing in antigenic structure, as well as toxin content and virulence, may have dissociated from one strain, several partial antigens should be present in any vaccine. Hemorrhagic toxin did not appear to be important for the immunizing effect or virulence of any strain.—*Serological studies on H. pertussis, H. parapertussis, & H. bronchisepticus (preliminary report), E. K. Andersen, Acta path. et microbiol. Scandinav., 1952, 30: 54.*—(*H. G. Turner*)

Cardiorespiratory Effects of Stress.—Exercise was performed by normal subjects during a standardized stress and during the unusual stress of an increased work load of 20 per cent-

grade walking or a lowered inspired oxygen concentration or both. Although ventilation, heart rate, and oxygen debt were increased, the breathing reserve and the physical-fitness index were diminished by these unusual stresses. Whereas the respiratory efficiency was highest with the standard stress, either hypoxia or excessive work demand lowered it. The greater the work load, the longer was the time required by the heart rate for recovery of its resting level. A lower oxygen consumption during exercise and a higher oxygen debt were observed with the more severe degrees of hypoxia. Symptoms of coronary insufficiency were not encountered. Physical signs of circulatory strain were observed transiently during early recovery in some subjects. The reduction in the physical-fitness index in normal subjects who were under unusual stresses was comparable to that observed in the patients who were moderately disabled by circulatory or pulmonary insufficiency (Author's summary).—*Observations of cardio-respiratory performance in normal subjects under unusual stress during exercise, R. A. Bruce, F. W. Lovejoy, & M. E. McDowell, A. M. A. Arch. Indust. Hyg. & Occup. Med., 1952, 6: 105.*—(*T. H. Nochren*)

Experimental Extracorporeal Circulation.—The life of experimental dogs was maintained by homologous lungs and a membrane pump while the heart and lungs of the animal were functionless for short periods; such animals survived the experiment without evidence of organ damage. The heart and lungs were resected *en bloc* from a heparinized donor dog and the heart, except for the left auricle, was removed. The trachea was connected to an oxygen source and breathing bag. The pulmonary artery and left auricle of the donor animal were connected through a pumping system with the vena cava and femoral artery, respectively, of the heparinized recipient animal. The superior and inferior vena cava of the recipient dog were occluded by ligations during the experiment. Oxygenation of the blood by the homologous lungs was optimal; the removal of carbon dioxide was also accomplished without difficulty. Collection, preparation, and handling of heparinized blood caused some hemolysis, plasma hemoglobin levels of 60 mg. per 100 cc. or more being found. In recent trials, 5 of 8 consecutive dogs have been maintained with homologous lungs and a mechanical heart while their own cardiorespiratory function was suspended for twenty-five to forty-five minutes. The last 4 consecutive dogs were perfused without failure. The surviving dogs returned to normal behavior.—*Successful experimental maintenance of life by homologous lungs and mechanical heart, H. W. Fischer, H. Albert, W. L. Riker, & W. J. Potts, Ann. Surg., September, 1952, 136: 475.*—(*M. J. Small*)

Coronary Blood Pressure in Shock.—Direct intracoronary and peripheral arterial pressure determinations have been made in dogs with graded stages of hypotension from acute hemorrhage. The decline in coronary pressure in progressive hemorrhage followed the same curve as that in the major arteries. Complete occlusion of the thoracic aorta caused a prompt rise in the coronary pressure in mild, moderate, and even severe hypotension. Compression of the abdominal aorta was less effective in raising the coronary pressure. Least effective, but still beneficial, was the elevation (Trendelenburg) of the foot of the operating table. Rapid intra-arterial or intravenous transfusions quickly elevated the coronary pressure in mild and moderate stages of shock. In extreme hypotension from hemorrhage, intra-arterial transfusion was the most effective method of raising the coronary pressure and restoring the general circulation (Authors' summary).—*The reaction of the coronary blood pressure to graded stages of shock (hemorrhage), J. R. Veal, A. S. Russell, & F. S. Ashburn, Ann. Surg., September, 1952, 136: 485.*—(*M. J. Small*)

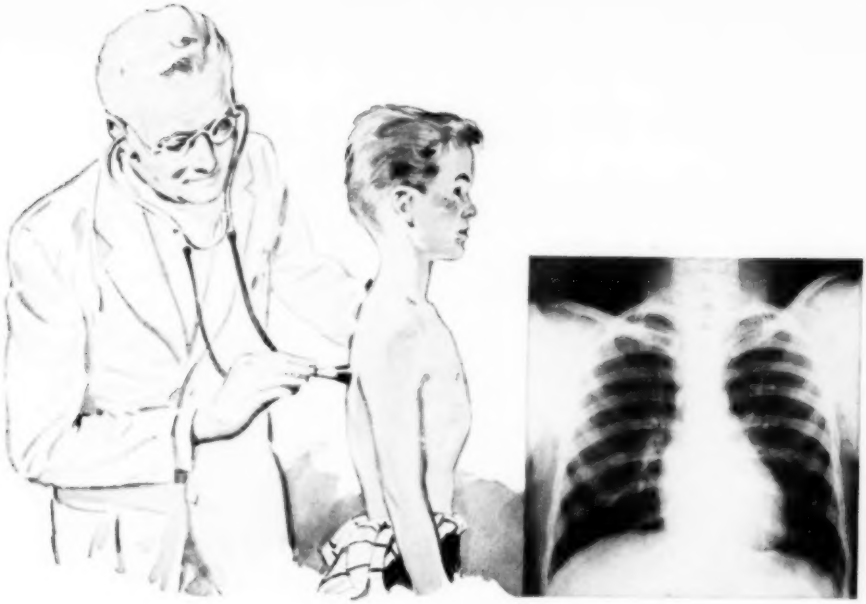
PUBLIC HEALTH AND EPIDEMIOLOGY

Five-Year Minifilm Program.—A five-year study with a mobile roentgenographic unit has been completed in Vanderburgh County, Indiana. This survey is unique in that (*1*) the

project was continuous, (*2*) the operation of the unit and the follow-up were carried on by the same organizations, (*3*) stereoscopic roentgenograms permitted prognostication of both active and inactive lung lesions, and (*4*) the project was self-supporting. Of 70,877 individuals roentgenographed on 4- by 10-inch stereoscopic minifilm, 59,716 (84 per cent) were negative for the reinfection type of pulmonary tuberculosis and 2,910 (4 per cent) had the reinfection type of pulmonary tuberculosis, of whom 2,866 (4.04 per cent) had inactive disease by roentgenographic examination, while 44 (0.06 per cent) had active disease. Another 31.4 patients per 1,000 showed other chest pathology and abnormalities. Among the more important were lesions of the heart and aorta, 10.3 per 1,000; substernal thyroid, 0.4 per 1,000; lung tumors, 0.1 per 1,000; and congenital cystic disease, 0.04 per 1,000. It is believed that repeated roentgenographing, year after year, is essential for adequate case finding since tuberculosis becomes active periodically. Continuous roentgenographing promotes continuous education and follow-up, which cannot be achieved if the examinations are sporadic. It is also difficult if one organization is responsible for taking the roentgenograms and another is responsible for the follow-up program.—*Evaluation of a five year minifilm program, P. D. Crimm, Am. J. Roentgenol., August, 1952, 68: 249.*—(*T. H. Nochren*)

Mass Survey in France.—A mass survey, using a mobile unit, was conducted through several factory areas in France. Photoroentgenograms on 8- by 8-centimeter film were taken. Despite advance publicity, only 70 per cent of the population responded. Of a total of 33,842 films, 23,903 were normal. The percentage of clinically significant tuberculosis was only 1.89, but in certain sections was as high as 5 or 6 per cent, notably in an area of ceramic industry where the rate of silicosis was also high. It is concluded that the relative cheapness of the methods warrants the discovery of even a few cases, especially as these are usually early and relatively amenable to treatment.—*Valeur de la radiophotographie comme moyen de dépistage systématique des affections thoraciques, R. Coursault, Poumon, May, 1952, 8: 415.*—(*F. S. Lansdown*)

Mass Roentgenography in Yugoslavia.—During 1949, 259,000 persons were roentgenographed by the twelve modern mobile units and a like number of smaller units of the Yugoslavian Public Health Service. The results probably are unreliable because (*1*) easily organized groups such as students, sailors, and laborers were examined and no general survey of the population was made; (*2*) preparations were inadequate and field procedures were poorly carried out; and (*3*) the films were not properly evaluated nor were suspected cases properly followed. These defects can be corrected by better field organization, closer cooperation with the local health services, better preliminary propaganda, and more prompt reading of the films with better follow-up techniques. It is essential that detected cases be treated and the nearest antituberculous dispensary must be prepared to act. The Statistical Service must help prepare the epidemiologic review.—*A critical review of mass-radiography (Yugoslav), R. Neubauer, Tuberkuloza, January-April, 1952, 4: 148.*—(*J. Havsky*)



A drug of choice in tuberculosis

As therapeutically active as streptomycin, CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK is less toxic to the vestibular apparatus, minimizes pain and swelling on injection, and may be used even in some patients allergic to streptomycin.

This preferred product is available in dry powder form and in convenient ready-to-inject form as SOLUTION OF CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK.

PARA-AMINOSALICYLIC ACID MERCK (PAS), when used in combination with CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK, prolongs the effective period of antibiotic therapy by inhibiting or delaying the development of bacterial resistance.

Crystalline Dihydrostreptomycin Sulfate Merck

COUNCIL ACCEPTED

Research and Production for the Nation's Health

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY

FOR QUICK, ECONOMICAL CHEST X-RAYS

Use Fairchild's 70-mm Fluoro-Record Cameras

FOR ROUTINE CHEST X-RAYS

The 70-mm Fluoro-Record Cut-Film Camera provides two single chests or one stereo pair on a single sheet of 2⅛ x 6½ in. cut film. Pictures can be 2½ x 2½ or 2½ x 3 in. Exposure is automatic. Film size (equivalent to 70 mm) keeps costs down. Processing, reading, handling, and filing are simplified. Camera is available on 70-mm admission units or can be adapted for many leading types of equipment.

TO SPEED MASS RADIOGRAPHY

The 70-mm Roll-Film X-Ray Camera incorporates features recommended by public-health officials, radiologists, and x-ray equipment manufacturers. Keeps costs down because film size means economical processing and savings in time and filing space. One technician can x-ray up to 150 chests per hour. Film automatically advances for each exposure. Accommodates up to 100 ft. of roll film.

FOR VIEWING UNDER IDEAL CONDITIONS

Fairchild X-Ray Film viewers provide just the right amount of light for comfortable viewing regardless of room lighting conditions or varying exposure densities. The 70-mm roll-film viewer (left) permits continuous rapid scanning in either direction of a 100-ft. roll. Stereo viewer (right) gives full three-dimensional effect to stereo pair on either roll or cut 70-mm film. The 70-mm cut-film viewer (not shown) handles 2⅛ x 6½ strips. A-c or d-c operation.

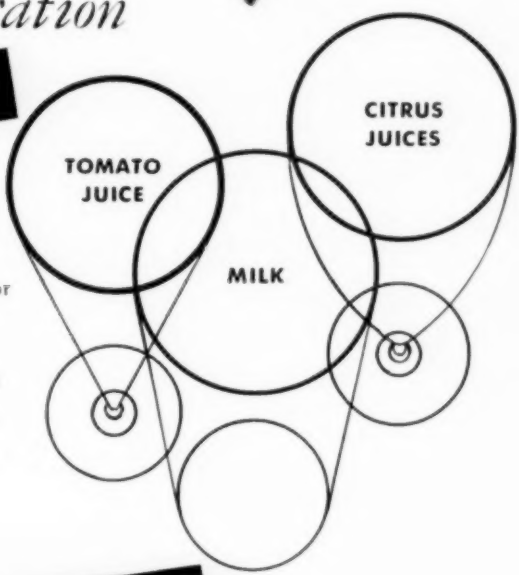
• *Complete information about these and other Fairchild x-ray units and accessories, such as roll-film developing units, all of which are available from your x-ray equipment supplier, can be obtained by writing to* Fairchild Camera and Instrument Corporation, 88-06 Van Wyck Boulevard, Jamaica 1, New York, Department 160-28C1.

FAIRCHILD

X-RAY EQUIPMENT AND ACCESSORIES

In Tuberculosis Therapy Choose The Most Versatile- Most Convenient- Most Accurate Method of PAS Administration

Hellwig's PACKETTES



With Hellwig's PACKETTES the preparation of a single dose of P.A.S. no longer entails measuring powder or counting tablets. No chance of inaccuracy. Each envelope is pre-weighed. Each PACKETTE contains 4.13 grams of *neutral* Sodium Para amino Salicylate Dihydrate (4.13 grams being equal to exactly 3.0 grams of *free* Para amino Salicylic Acid).

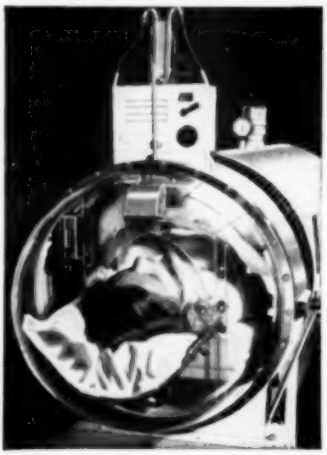
50 PACKETTES IN A BOX

Also available in Junior Size for Children —

Hellwig, Inc.

209 E. Chestnut St.
Chicago, Illinois
Saranac Lake, N. Y.

EMERSON
LUNG IMMOBILIZER



In the "equalizing pressure chamber" developed by Alvan L. Barach, M.D., the patient is enabled to cease completely all breathing motion, while a rhythmic alternation of air pressure and partial vacuum (+ and — 60 mm. Hg) produces effective pulmonary ventilation. This total lung rest has been found to promote closure of cavities in cases unresponsive to other forms of accepted therapy.

Addressing the College of Chest Physicians in 1950, Dr. A. L. Barach of New York and Dr. G. L. Bellis of Wisconsin presented reports on the treatment of 67 advanced cases (73 percent). More recently Drs. William Grosfeld and James C. Nash of Alabama have reported results in a series of 23 cases.

Please write for reprints

J. H. EMERSON CO.

22 Cottage Park Ave., Cambridge 40, Mass.

Close-up of Eye Taken with New Exakta "VX" Camera

New Model With Pre-Set Diaphragm Control

35mm EXAKTA "VX"

Single Lens Reflex Camera For Parallax-Free Medical Photography

The Exakta, with instantly interchangable lenses, is widely used in the study of tuberculosis for every type of medical and research photography. Its unique through-the-lens viewing system assures absolutely correct "on-the-subject" photographs, in extreme close-ups or through the microscope. In addition, this world famous medical camera is regularly used for preliminary, developmental, and end result pictures of patients, for copying X-rays, and for making color transparencies—a necessity for recording and lecturing.

With f2.8 Zeiss Tessar "T" Coated Lens with Pre-Set Diaphragm	**$269.50**
Penta-Prism Eye Level Reflex Viewfinder	**50.00**
Extension Tube Set	**24.00**
Microscope Adapter	**29.50**

Write Dept. 1111 for free descriptive booklet "VX" on camera and accessories and brochure on close up technique with the Exakta.

EXAKTA CAMERA CO. **46 West 29th St., New York 1, N. Y.**

Exclusive Sales And Service Organization In The U.S.A. For Ihagee Camera Works, Germany

THE Syko-Steril MATTRESS

Eliminates rubber sheets and plastic covers because—it can be cleaned with soap and water and treated with hospital deodorants or disinfectants without damage.

Actual tests in mental hospitals have proved it *practically indestructible* by physical effort without the use of a cutting edge. The coating will actually get tougher with time. It is impervious to body liquids, and non-toxic to the skin. Cotton sheets will not crawl or wrinkle under the body.

Hospitals report—"Everything claimed for them" and "placing another and larger order for Syko-Steril mattresses".

We will replace any mattress that fails in the claims we make for it.

Write, or send a trial order, direct to the factory office—

The Rest-Rite Bedding Co.

Mattresses since 1898

207 North Main St. **Mansfield, Ohio**

WOODWARD

MEDICAL PERSONNEL BUREAU

Ann Woodward, Director

185 North Wabash Ave. Chicago 1

MEDICAL TECHNOLOGISTS: (a) Experienced, 100-bed general hospital, fine facilities including blood bank; to $4800; Ohio. (b) Chief, active laboratory serving several hospitals; $3500 up; New York. (c) Senior, well-equipped modern clinic-hospital; $3600; New Mexico. (d) Administrative duties, B.S. degree, experienced, 275-bed general hospital; $4200; Missouri. (e) 200-bed hospital, 5-day week, resort town, Michigan; to $4000; meals and laundry. (f) Director, degree required, registered, for 100-bed Michigan hospital; $4800. (g) Chief, female, small approved hospital, excellent salary, Massachusetts. (h) Head, female, private laboratory, 4 technicians in department; to $4200; Iowa. (i) New 200-bed general hospital with latest equipment, 5-day week; to $4200; Indiana. (j) 150-bed approved hospital, 44-hour week, Rocky Mountain resort town; to $4200. (k) College trained, qualified in medical and public health, for active laboratory; to $4800; Arizona. (l) Registered, female, 2-doctor private office, 5-day week, Washington. (m) Registered, 150-bed general Texas hospital, fine opportunity. (n) Experienced, registered for private or hospital laboratory; to $5000; Texas. (o) 200-bed approved Ohio hospital, 40-hour week, 6 technicians in department; to $3600.

BIOCHEMISTS: (a) M.S. or Ph.D. degree required, 375-bed general hospital, Chicago suburb; $6000. (b) Assistant Director with degree in biochemistry or bacteriology, laboratory serves several hospitals, opportunity for further education; $5000 up, New York. (c) Head department of 225-bed teaching hospital, excellent personnel policies, Northwest.

CHEMIST: Experienced, 600-bed hospital, university town, excellent salary; southeast.

BACTERIOLOGISTS: (a) Capable of organizing department of 250-bed Indiana hospital, fine personnel policies. (b) For 200-bed Michigan hospital, fine facilities; $3600 with meals and laundry.

HISTOLOGISTS: (a) Private laboratory, resort town on Lake Michigan; fine opportunity. (b) Experienced, active laboratory, new and fully equipped, university town, east.

HEMATOLOGISTS: (a)Research department of 275-bed approved general Ohio hospital; $4200.

LABORATORY & X-RAY: (a) New, modern, small hospital, resort town; $4800; Arizona. (b) New 50-bed general Florida hospital, modern facilities, excellent salary and meals. (c) Active hospital laboratory, 40-hour week, industrial area; $4200; Pacific northwest.

MANY other attractive opportunities. Please send for Analysis Form so that we may prepare an individual survey for you. WOODWARD Medical Bureau, 185 North Wabash, Chicago, Illinois.

POSITIONS AVAILABLE AND WANTED

WANTED: Experienced assistant medical director or resident physician. A.C.S. approved 280-bed TB hospital. Excellent Salary. Physician must be eligible for Michigan license. Box No. 114, American Review of Tuberculosis, 280 Madison Avenue, N. Y. 16, N. Y.

WANTED: Resident for 40-bed tuberculosis unit in a contagious hospital located within city limits. Salary open. Apply to Superintendent, Charles V. Chapin Hospital, Providence, R. I.

POSITIONS AVAILABLE: Applications are invited for positions of Resident, Assistant Resident, and Junior Interne at Grace Dart Hospital, 6085 Sherbrooke, East, Montreal, P. Q. This is a 145-bed tuberculosis hospital approved by the American College of Surgeons. All methods of Medical and Surgical treatment are used. Duties of Resident to begin immediately. Others on July 1st, 1955. Apply to Medical Director.

PHYSICIAN, senior, local Sanatorium eastern New York. Complete medical and surgical program. Medical school and general hospital affiliation. Beginning salary, seven thousand. Modern home. Box 114, American Review of Tuberculosis, 280 Madison Avenue, N. Y. 16, N. Y.

WANTED: Resident Physician, Tuberculosis Experience Essential. Call or Write Deborah Sanatorium, Brown's Mills, New Jersey.

Present Concepts of Rehabilitation in Tuberculosis

by **NORMAN C. KIEFER, M.D.**

420 pages, cloth cover $3.50

In this volume there is brought together, for the first time, an accurate summary of world research and achievement in every area of rehabilitation during the last decade.

More than 1,000 original papers are abstracted in this book, and in every case the salient features of each have been brought together in classified sections to provide a complete picture of approaches, procedures, and results.

A bibliography of more than 1,000 items supplies reference to basic sources, and a particularly comprehensive index facilitates the location of specific information.

Your order can be filled promptly.

NATIONAL TUBERCULOSIS ASSOCIATION

1790 Broadway, New York 19, N. Y.

New NTA Publication

Pennsylvania Pioneers

AGAINST

Tuberculosis

By Esther Gaskins Price

294 Pages *Cloth Bound* *$5.00 a Copy*

In this fully documented volume, there are brought together for the first time the stirring facts about the inception, development, and fruition of one of the most successful health crusades in history.

When this crusade started, tuberculosis was claiming human lives at the rate of more than 20,000 in a single decade in Philadelphia alone. Popular superstitions, medical conservatism, the hostility of landlords, industrialists and politicians, were some, but by no means all, of the difficult road blocks which confronted the pioneers.

Original Sources

Utilizing the proceedings of some of the most important medical meetings of the 19th century—the archives of the Pennsylvania Tuberculosis and Health Society and public health departments, newspaper files, and family records—PENNSYLVANIA PIONEERS AGAINST TUBERCULOSIS gives the historic details of the long drawn out battle waged by pioneers in the tuberculosis control movement.

This battle, spearheaded by Lawrence Flick and a small but forward-thinking group of earnest co-workers, finally led, among many other specific results, to the creation of the original tuberculosis society in the United States and the establishment of the first institution in medical history to concentrate on the prevention and treatment of a single illness.

Readers of the American Review of Tuberculosis will find in this book interesting and valuable background data, never before available, covering the critical period in which effective health control measures first began to assume their present shape.

Send your order today to:

National Tuberculosis Association, 1790 Broadway, New York 19, N. Y.

Additional postage outside U.S. and Canada, 50 cents a copy.

NATIONAL TUBERCULOSIS ASSOCIATION

ANNUAL MEETING **MAY 18–22, 1953**

LOS ANGELES, CALIFORNIA

The annual meeting of the National Tuberculosis Association will be held in Los Angles, California, May 18–22, 1953. The Hotel Statler and the Biltmore Hotel will be headquarters.

Some 1500 rooms have been promised by the hotels listed below for the accommodation of those attending the meeting. Arrange to share a twin bed room if possible.

Application for room reservations should be made directly to the hotel of your choice.

HOTEL	ADDRESS	SINGLE	TWIN	SUITES
Alexandria	210 W. 5th Street	$4.00- $8.00	$7.00-$10.50	$12.50-$25.00
Biltmore	515 S. Olive Street	$7.00-$11.50	$10.50-$14.50	$17.00-$33.00
Clark	426 S. Hill Street	$4.00- $6.00	$6.00-$ 8.00	$12.00-$18.00
Commodore	1203 W. 7th Street	$3.50-up	$6.00-up	$10.00-up
Hayward	206 W. 6th Street	$4.00- $6.00	$6.50- $8.00	$9.00-$15.00
Lankershim	230 W. 7th Street	$3.50- $5.00	$6.00- $7.50	$10.50
Mayfair	1256 W. 7th Street	$4.50-up	$7.50-up	$17.50
Mayflower	535 S. Grand Avenue	$5.25- $8.00	$5.75- $9.00	$14.00
Ritz Flower	813 S. Flower Street	$4.00- $5.00	$5.00- $6.00	—
Savoy	601 W. 6th Street	$4.00- $5.00	$5.50- $6.50	$8.00- $8.50
Statler, Wilshire and Figueroa		$6.50-$14.00	$10.00-$20.00	Not rated yet

IMPORTANT ANNOUNCEMENT

THE AMERICAN REVIEW OF TUBERCULOSIS has made available to its readers a section devoted to classified advertising pertaining to positions available and wanted. Since there have been so many requests for this type of service in the tuberculosis field, the Editorial Board of THE AMERICAN REVIEW OF TUBERCULOSIS decided to include a classified section at a nominal charge for each entry.

- **Cost per advertisement of 25 words or less will be $3.50, additional words 15 cents each.**
- **Bold Face Semi-display will be $5.00 per insertion for 25 words or less, additional words 20 cents each.**
- **Post Office Box numbers will be an additional 75 cents per advertisement.**
- **Address all classified advertisements, with check or money order enclosed, to:**

THE AMERICAN REVIEW OF TUBERCULOSIS

280 MADISON AVENUE **NEW YORK 16, N. Y.**

Murray Hill 5-8140

THE Panray CORP.

Notes on TUBERCULOSIS CHEMOTHERAPY

February, 1953

PAS THERAPY WITH MINIMUM SIDE EFFECTS

Many hospitals and TB specialists have obtained gratifying clinical response with BUFFERED PARASAL® tablets—an exclusive formulation of para aminosalicylic acid that (1) minimizes GI upsets and PAS intolerance, (2) contains no sodium or sugar, (3) permits *2 tablets to replace 3* of the usual sodium PAS, and (4) is consequently more convenient and economical to administer.

The unique buffering action is non-systemic, effectively maintains stomach pH at optimal pepsin activity for 2 to 3 hours, and avoids the "acid rebound" that often occurs after ingestion of systemic antacids.

Product No. 744.

PARASAL-INH . . . COMBINATION THERAPY IN 1 TABLET

Isoniazid is now finding its place in combined therapy with PARASAL and streptomycin. For more convenient administration, we have developed a combination tablet, BUFFERED PARASAL-INH; each tablet contains 0.5 Gm. PARASAL and 12.5 mg. ISONIAZID 'PANRAY.' (For effect of buffering action, see "A" above.)

Here are the dosage equivalents of the new tablet:

Buffered PARASAL-INH total daily tablets:	Yields total daily PAS	ISONIAZID
16	8 Gm.	+ 200 mg.
18	9	+ 225
20	10	+ 250
24	12	+ 300

Both PARASAL and ISONIAZID 'PANRAY' are AMA Council Accepted, but the *combination* is still on trial and is available for investigational use only.

Product No. 790.

STREP-INH COMBINATION THERAPY

STREPTONIAZID, a sterile solution of dihydrostreptomycin and ISONIAZID 'PANRAY' is another Panray drug developed to make combination therapy as simple and as foolproof as possible. This parenteral form is packaged in 4-cc vials, each containing 1 Gm. of dihydrostreptomycin and 150 mg. of ISONIAZID.

Because the combination is quite new, STREPTONIAZID like BUFFERED PARASAL-INH described above, is available for investigational use only.

Additional information is available for all three Panray products discussed above.

Product No. 780.

Research and Production for the Medical Profession

THE Panray CORP.

340 Canal Street, New York 13, N. Y.